Ray Peat's Newsletter

"The attitude of great poets is to cheer up slaves and horrify despots" ... Walt Whitman

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Aging Eyes, Infant Eyes, and Excitable Tissues

The eyes and the lungs are sensitive tissues that are easily harmed by inappropriate environmental exposure. They are especially sensitive in infancy and old age.

For 60 years there have been controversies about the cause of retinopathy of prematurity, which has blinded tens of thousands of people.

Degeneration of the retina is the main cause of blindness in old people. Retinal injury is caused by ordinary light, when the eyes are sensitized by melatonin, prolactin, and polyunsaturated fats. Bright light isn't harmful to the retina, even when it is continuous, if the retina isn't sensitized.

Melatonin and prolactin are induced by stress, and darkness is a stress because it impairs mitochondrial energy production.

The polyunsaturated fats which accumulate in the brain and retina damage mitochondria.

Iron, which accumulates prenatally, and then again with aging, reacts with unsaturated fats during stress to destroy cells.

The popular supplements melatonin, tryptophan, fish oils, St. John's wort, and the various omega -3 oils, all increase the risk of retinal light damage and macular degeneration. Serotonin uptake inhibiting antidepressants are suspected to be able to cause it.

Processes similar to those that damage the over-sensitized retina can occur in other cells, as a result of stress. The substances that sensitize the retina to light-damage, can also increase the incidence of new or metastatic cancers.

Iron supplements and the use of supplemental oxygen, especially with a vitamin E deficiency exacerbated by excessive unsaturated fats in the diet, are still commonly used exactly when they can do the most damage.

One of the recognized achievements of biology has been the demonstration of life's universality, in the sense that organisms of all sorts use the same fundamental genetic code, and that yeasts, lizards, apes, and people have remarkably similar cellular systems, as well as a great amount of genetic similarity.

There has been another, less well recognized, sort of convergence going on in physiology and pathophysiology. Hans Selye's concept of stress, "the syndrome of being sick," Otto Warburg's argument that a "respiratory defect" was behind all kinds of cancer, and the idea of free radical damage as a common factor in disease and aging, helped to create a more general way of looking at the nature of disease that superceded medicine's theories of disease pathogens and genetic mutations, which created thousands of "disease entities," none of which had much to do with the individuality of the patient or his environment.

The understanding that plants and animals have much biochemistry in common has gradually changed the assumptions of the science establishment, which until recently insisted that only "ionizing radiation" could affect animals or other organisms that lacked chlorophyll--and insisted that ionizing rays acted only on the DNA. Visible light, the textbooks said, was not "chemically active," and so couldn't possibly affect animals' cells. In animals, coloration was seen mainly as decoration and disguise, rather than as a functional part of their biochemistry.

(Chemically, the meaning of "a pigment" is that it's a chemical which selectively absorbs radiation. **Old observations such as Warburg's, that visible light can restore the activity of the "respiratory pigments," showed without doubt that visible light is biochemically active.** By the 1960s, several studies had been published showing the inhibition of respiratory enzymes by

blue light, and their activation by red light. The problem to be explained is why the science culture simply couldn't accept crucial facts of that sort.)

The retina, of course, was allowed (in the views of mainline science) to respond to ordinary light, but the few people who studied the biological effects of seasonal or daily cycles of light have until recently stayed very close to the nerve pathways leading from the retina to the pineal gland, because those pathways could be described in terms of an evolutionarily specialized "third eye." Even with a doctrine of a genetically specialized link between the retina and a little of the animal's physiological chemistry, the great, slow-witted science establishment has done its best to avoid thoughts of any deep interaction between an organism and its environment, by insisting that the organism runs according to a genetically determined "clock" which is located in a few cells in a certain area of the brain, and that nervous impulses from the retina have only the small privilege of "setting the clock."

It didn't matter to the academic and medical worlds that a professor, Frank A. Brown, had long ago disproved the idea of an innate genetic "clock," because philosophy is much stronger than evidence. Leibniz had said that everything in the world runs on its own inner clock, without needing to perceive its surroundings, and this idea that everything in the world is a "windowless monad" resonated through the world of science, because it justified the pompous authoritarian attitudes of the experts who knew that anything that wasn't already in their heads couldn't be considered knowledge. **If an organism's "essence is contained in its genes," then it clearly doesn't interact in any meaningful way with most of its environment.** This is the sort of culture that imbued research on the biology of light cycles.

When I moved from Mexico, first to Montana and then to Oregon in 1966, I became very conscious of how light affects the hormones and the health. (For example, in Montana I experienced an interesting springtime shedding of body hair.) Many people who came to cloudy Eugene to study, and who often lived in cheap basement apartments, would develop chronic health problems within a few months. Women who had been healthy when they arrived would often develop premenstrual syndrome or arthritis or colitis during their first winter in Eugene.

The absence of bright light would create a progesterone deficiency, and would leave estrogen and prolactin unopposed. Beginning in 1966, I started calling the syndrome "winter sickness," but over the next few years, because of the prominence of the premenstrual syndrome and fertility problems in these seasonally exacerbated disorders, I began calling it the pathology of estrogen dominance. In the endocrinology classes I taught at the National College of Naturopathic Medicine, I emphasized the importance of light, and suggested that medicine could be reorganized around these estrogen-related processes. If the sparrows of Times Square mated in the winter because of the bright lights, it seemed clear that bright artificial light would be helpful in regulating human hormones.

In our lab at the University of Oregon, our hamsters would try to hibernate, even though they were in temperature-controlled laboratories with regular cycles of artificial light. (The ceiling lights provided only dim illumination inside their cage boxes, so they were probably in a chronic state of light deprivation, which probably increased their sensitivity to the weak environmental cues that Frank Brown had investigated, possibly microwaves that easily penetrated the lab walls.) During the winter, when they were infertile, I found that their thymus glands practically disappeared. The mechanism seemed to include the increase of pineal gland activity (probably increasing melatonin synthesis) in the winter, under the intensified activity of the "sympathetic nervous system" (with increased activity of adrenalin and other catecholamines), and the melatonin was apparently a signal for suppressing fertility during the stressful winter. In some animals (Shvareva and Nevretdinova, 1989), estrogen is increased during hibernation, contributing to the reduction of body temperature.

In 1994 A.V. Sirotkin found that melatonin inhibits progesterone production but stimulates estrogen production, and it's widely recognized that melatonin generally inhibits the thyroid hormones, creating an environment in which

fertilization, implantation, and development of the embryo are not possible. This combination of high estrogen with low progesterone and low thyroid decreases the resistance of the organism, predisposing it to seizures and excitotoxic damage, and causing the thymus gland to atrophy.

Cyclical exposure to melatonin can have an effect on the reproductive system opposite to that of chronic exposure, and the way exogenous melatonin is delivered to the animal can have unexpected effects on the actual amount of melatonin circulating in the blood (Wright and Alves, 2001). The actual amount of melatonin in the tissues, its relation to the normal cycling of the animal, and the influence of temperature, are often disregarded in melatonin research, making it hard to interpret many of the publications.

There is a lot of talk about melatonin's function as an antioxidant, but, like so many other "antioxidants," melatonin can act as a pro-oxidant at physiologically relevant concentrations; some studies have found that it, like estrogen, increases the activity of the pro-oxidative free radical nitric oxide (which acts like melatonin on pigment cells, causing them to lighten). The promoters of estrogen are also making claims that estrogen is a protective antioxidant, though that isn't true of physiological concentrations of the estrogens, which can catalyze intense oxidations. The market culture seems to guide most research in these substances.

Almost any kind of stress increases the formation of melatonin.

In some animals, melatonin has been shown to be responsible for whitening of the hair during the winter. In some species it acts directly on the pigment cells, but in other species it seems to inhibit the action of the melanocyte stimulating hormone.

In snowy climates, it's "ecologically" rational for animals to turn white in the winter, for camouflage. But tadpoles also turn white in the dark, or under the influence of melatonin, and the biological meaning of that isn't so clear. It's possible that being white would reduce their loss of heat through radiation, but I think it is more likely that it relates to an increased ability of weak radiation to penetrate their tissues, rather than being stopped near the surface by the melanin in the skin. The absence of melanin makes them more sensitive to light. Bright light suppresses their melatonin, and makes them turn dark brown or black, and this protects them from bright sunlight.

In the retina, melatonin increases the sensitivity of the cells to dim light. It, along with prolactin, another nocturnal hormone, helps to produce dark adaptation of the eyes.

Melatonin increases the concentration of free fatty acids during the night (John, et al., 1983; John and George, 1976)), so it's interesting that one of the long-chain highly unsaturated fatty acids, DHA (docosahexaenoic acid), also increases the light sensitivity of the retina.

Melatonin lowers body temperature, causes vasoconstriction in the brain, heart, and other organs, and slows reactions. An antagonist to melatonin acts as an antidepressant, reducing "behavioral despair" resulting from stress. (Dubocovich, et al., 1990.) So, in the behavioral sense, melatonin reduces sensitivity, yet it increases the eyes' sensitivity to light, causing them to be injured by light that would otherwise be harmless.

Since a hibernating animal under the influence of melatonin can become very cold, the light-sensitizing function of melatonin is probably related to the biological need to be roused out of the torpor occasionally. (Hibernators apparently have to warm up occasionally to sleep in the ordinary manner.) Melatonin is said to intensify dreaming, which is part of the process of arousal from sleep.

All of the stress-related hormones increase during the night. One of the ways these hormones of darkness act is to increase the sensitivity to light, in a process that is an important adaptation for organisms in dim light. In the night, our ability to see (and respond to) dim light is increased. But dark-adapted eyes are very sensitive to injury by bright light. Light that ordinarily wouldn't harm the eyes, will do serious damage when the eyes are dark adapted.

In thinking about the effects of stress and oxygen deprivation, I read the studies demonstrating that the formation of the oxygen-wasting age pigment, lipofuscin, is increased by estrogen, by

oxygen deprivation (in carp living below the ice, or even in fetuses), by metals such as iron, by x-rays, and by highly unsaturated fats.

Free fatty acids that are mobilized from storage tissues in the night and in the winter also tend to increase with aging, as the ability to tolerate stress decreases. Poor circulation and lipofuscin tend to be associated, in a vicious cycle. This means that the retina becomes easier to injure by light in old age, for some of the same reasons that the infant's retina is susceptible.

The fetus accumulates a very large amount of iron, and it absorbs melatonin from the maternal circulation. Prolactin is sometimes elevated in the newborn. Premature babies are often given extra oxygen, which tends to cause vasoconstriction by displacing carbon dioxide. Melatonin's ability to cause vasoconstriction means that stress makes supplemental oxygen more toxic. Synthetic glucocorticoids are often given to premature babies, adding to the risk of retinal damage.

When the mother has been given iron supplements during pregnancy, along with unsaturated oils in the diet, the baby is likely to be born with a vitamin E deficiency and suppressed thyroid function, increasing the probability that it will be jaundiced, leading to treatment of the jaundice with exposure to very bright light.

Although Yandell Henderson had already, in 1928, explained the need for carbon dioxide to be used with oxygen for resuscitating infants or adults, medical researchers and hospital workers could never accept the idea, probably because of a fundamental misunderstanding of the Henderson-Hasselbalch equation. Animal experiments show that supplemental oxygen, without carbon dioxide, causes vasoconstriction, reducing the tissues' supply of glucose as well as oxygen. In combination with too much light, especially blue light, it damages the retina. At hyperbaric pressure, oxygen causes seizures, as well as damage to the lungs and other tissues.

The contribution of bright light to retinal damage in babies has been denied in several recent publications, and these articles undoubtedly provide useful material for defense lawyers to use when hospitals are sued for causing blindness. One publication based on experiments with kittens concludes that bright light does not harm the newborn's retina, but the comparison is between continuous light and intermittent light, rather than between bright light and dim light. Twelve hours of total darkness, rather than sparing the eye by reducing its exposure to light, would sensitize the eye. The only reason such appalling things can be published is that their conclusions protect the hospitals.

A few good studies of the effect of bright light on the retina, and the fact that dark-skinned people with more protective pigment in their eyes have a lower incidence of retinopathy of prematurity, make it clear that the ordinary laws of physics and chemistry actually do apply to the infant eye.

Light and stress, especially with excess iron, damage the retina when the cells contain too much PUFA, since these fats react with light and free radicals. The nocturnal/stress hormones, especially prolactin and melatonin, make the retina more sensitive to light, and more easily damaged. (It's too much darkness that sets up the problem, since the eyes will adapt to excess light, but darkness increases their sensitivity.)

The use of lasers to operate on eyes produces intense inflammation of the eye, but even at low dose the diffusing light causes retinal/macular damage.

Cytochrome oxidase is one of the enzymes damaged by stress and by blue light, and activated or restored by red light, thyroid, and progesterone. It's a copper enzyme, so it's likely to be damaged by excess iron. It is most active when it is associated with a mitochondrial lipid, cardiolipin, that contains saturated palmitic acid; the substitution of polyunsaturated fats lowers its activity. Mitochondrial function in general is poisoned by the unsaturated fats, especially arachidonic acid and DHA.

Creating a "deficiency" of DHA, even when an oil of known toxicity is used to replace the omega -3 oils, prevents retinal damage from light. Despite evidence of this sort, Mead Johnson is going ahead with the marketing of its baby formula containing added DHA which is industrially extracted from algae. (Although the researchers who claim that DHA is beneficial haven't

answered my letters, a representative of the company that manufactures it did answer my question about the actual composition of the oil, and acknowledged that they don't have any idea what the minor ingredients might be.)

When animals are made "deficient" in all the exogenous polyunsaturated fatty acids, linoleic and arachidonic acid as well as linolenic and DHA, they become remarkably resistant to all sorts of stress and toxins.

The polyunsaturated fats make the lungs more sensitive to excess oxygen or hyperventilation, they make the eyes more sensitive to light, and they make the brain more sensitive to fatigue.

The use of synthetic glucocorticoid hormone is standard in treating very premature babies, although it is known to contribute to eye damage. This is because it is considered necessary to improve the lung function of premature babies with respiratory distress. But there is no clear evidence that it is beneficial for lung function in the long run, and very clear evidence that it damages the brain and other organs. There is widespread agreement regarding the use of the glucocorticoids ***prenatally*** to accelerate lung development in women who seem likely to deliver prematurely. Natural cortisol is a factor that promotes lung development prenatally. But cortisol is also a signal produced by a stressed fetus, that triggers the birth process. Cortisol, or the synthetic glucocorticoid, inhibits progesterone production, and stimulates estrogen production, activating uterine contractions and other processes that terminate the pregnancy.

Apparently, it doesn't occur to many people that administering the glucocorticoid triggers premature birth, creating the problem they are intending to treat.

Recognizing causal connections between premature birth and respiratory distress and retinopathy of prematurity, it would be obvious that the greatest effort should be made to prevent the problems by improving the health of pregnant women. Hospitals, however, are invested in high technology systems for treating these problems, and even though their results are dismal, they can't make money by getting pregnant women to eat enough protein to prevent preeclampsia, which is a major cause of premature birth, or by treating the problems with salt, magnesium, progesterone, thyroid, and aspirin when the women haven't had a good diet.

Historically, preeclampsia has been blamed on the mother's or fetus's "bad genes," and that cultural bias was the setting in which these high technology prenatal and neonatal systems developed. High technology "neonatology" derives from the same ideology that motivated Josef Mengele's genetic research in Auschwitz. The idea of genetic determination is still motivating resistance to reasonable preventive approaches.

Thyroid, i.e., T3, is very effective in accelerating lung development in the fetus, and it doesn't have any of the harmful effects of the synthetic glucocorticoids. It normalizes the hormones, increasing progesterone and decreasing estrogen, which are needed for full-term gestation, the opposite of the glucocorticoids' effects. While the cortisol-like drugs damage the brain and other organs, thyroid and progesterone protect them.

Old organisms, like newborns, are easily injured by all sorts of inappropriate excitation. As in premature babies, the aged eyes, lungs, and brain are especially sensitive to damage by stress. *But all organs are subject to the same kinds of damage.* Medical treatments for respiratory distress and macular degeneration in old people are often the same as those used so inappropriately for babies. ***The good health practices that can prevent the inflammatory and degenerative diseases can often make it possible for damaged tissues to recover, even in old age.***

The pituitary hormones, especially prolactin and TSH, are pro-inflammatory, and darkness increases TSH along with prolactin, so to compensate for a light deficiency, the pituitary should be well-suppressed by adequate thyroid. Armour thyroid or Thyrolar or Cynoplus, Cytomel, would probably be helpful. (Eye-drops containing T3 might be a way to restore metabolic activity more quickly.) Limiting water intake (or using salt generously) helps to inhibit prolactin secretion. The saturated fats protect against the body's stored PUFA, and keeping the blood sugar up keeps the stored fats from being mobilized. Aspirin (or indomethacin) is generally protective

to the retina, analogously to its protection against sunburn. Adequate vitamin E is extremely important. There are several prescription drugs that protect against serotonin excess, but thyroid and gelatin (or glycine, as in magnesium glycinate) are protective against the serotonin and melatonin toxicities. Copper and magnesium deficiencies predispose to retinal damage. Red light is protective, blue light (or u.v.) is harmful, so wearing orange lenses would be helpful. Progesterone and pregnenolone, by reducing the stress reactions, should be helpful--in the eye diseases of infancy and old age, as they are in the respiratory distress syndromes.

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Endocrinol Exp 1976 Jun;10(2):131-7. **Diurnal variation in the effect of melatonin on plasma and muscle free fatty acid levels in the pigeon.** John TM, George JC. Pigeons maintained on standard diet and held under 12 h daily photo-period in a controlled environmental room, were given intravenous injections of melatonin. A low dose (1.25 mg/kg body weight) of melatonin when given in the middle of the **scotophase, produced a significant increase in plasma FFA when estimated at 20 min and 90 min post-injection, whereas no significant change was seen with injections given in the middle of the photophase. No significant change in muscle FFA level was obtained either during the photophase or the scotophase** when estimated at 90 min postinjection. With a higher dose (5 mg/kg body weight) of melatonin given in the scotophase, on the other hand, a significant increase **in both plasma as well as muscle FFA levels was obtained at 90 min** post-injection but there was no effect on plasma FFA at 20 min or 90 min post-injection in the photophase and at 20 min in the scotophase. It is concluded that melatonin has a lipid mobilizing action in the pigeon when administered during the scotophase.

Arch Int Physiol Biochim 1983 Jul;91(2):115-20. **Diurnal impact of locomotory activity and melatonin and N-acetylserotonin treatment on blood metabolite levels in the rainbow trout.** John TM, Beamish FW, George JC. In rainbow trout forced to swim continuously at sustained speeds for six weeks, selected doses of melatonin or N-acetylserotonin (1.25 and 5.0 mg/kg body weight) injections caused no change in haematocrit. Melatonin did not produce any significant change in plasma glucose level either in the photophase or in the scotophase. However, diurnal variations were observed in the effect of melatonin on plasma free fatty acids (FFA). Melatonin was ineffective in causing **any change in plasma FFA level during photophase but during scotophase, the higher dose (5.0 mg/kg) produced an increase in FFA while the lower dose (1.25 mg/kg) had no effect, N-acetylserotonin administration produced diurnal** variation in its effect on both plasma glucose and FFA. The higher dose of N-acetylserotonin brought about a drop in plasma glucose level during photophase, but both doses were ineffective during scotophase. N-acetylserotonin produced no change in FFA during photophase, but during scotophase tended to lower FFA level. It is suggested that exercise shortens the time required to cause a hypoglycemic effect of N-acetylserotonin during photophase, blocks FFA release-inhibiting action of melatonin observed in photophase, and minimizes the time required for the FFA mobilizing action of melatonin in scotophase.

J Neural Transm 1977;40(2):87-97. **The adrenal medulla may mediate the increase in pineal melatonin synthesis induced by stress, but not that caused by exposure to darkness.** Lynch HJ, Ho M, Wurtman RJ.

Bull Acad Natl Med 2000;184(2):415-28; discussion 428-30. **[Pulmonary toxicity of oxygen]** [Article in French] Mantz JM, Stoeckel ME.

Br J Pharmacol 1977 Dec;61(4):607-14. **The action of melatonin on single amphibian pigment cells in tissue culture.** Messenger EA, Warner AE.

Oftalmol Zh 1989;(8):469-73. **[The early diagnosis, evaluation of treatment results and modelling of certain aspects of the pathogenesis of retinal dystrophy]** ; Mironova EM, Pavlova ON, Ronkina TI. The paper analyses results after a study of the functional state of pigmented epithelium and the retina in patients with a dry form of senile macular dystrophy as well as of experimental simulation of retinal dystrophy with the help of melatonin and its treatment by taurine. **Melatonin in 10(-3) M concentration leads to development of dystrophic changes** in pigmented epithelium and interacting with it structures, this being testified by remarkable lowering of EOG parameters and electron microscopic findings. Taurine in 10(-3) **M concentration blocks the action of exogenic melatonin as well as has a pronounced positive action on metabolism of dystrophic changes in the pigmented epithelium and photoreceptors. Examination of patients with different stages of a dry form of senile** macular dystrophy revealed statistically significant reduction of KA cEOG at the initial stage of the disease in the presence of normal ERG parameters. In 18% of patients, supernormal values of KA were recorded, that are likely to reflect the presence of "predystrophic hyperactivity" of the pigmented epithelium cells. In progression of the process, the further reduction of electrophysiologic values was recorded. The data obtained speaks about the important role of pigmented epithelium pathology in the pathogenesis of senile macular dystrophy and about high information value of the cEOG method for detection of early stages of the disease. It is believed that disturbances in melatonin metabolism can be one of causes leading to development of retinal dystrophy.

J Clin Endocrinol Metab 1977 Oct;45(4):768-74. **The effects of oral melatonin on skin color and on the release of pituitary hormones.** Nordlund JJ, Lerner AB. "We studied the effects of prolonged ingestion of melatonin, 1 g per day, on skin color and the serum levels of pituitary hormones in 5 human subjects with hyperpigmented skin. Melatonin lightened hyperpigmented skin of one patient with untreated adrenogenital syndrome, but had no effect on three patients' skin with idiopathic hyperpigmentation and one patient with treated Addison's disease."

Invest Ophthalmol 1976 Oct;15(10):869-72. **Hormonal influences on photoreceptor damage: the pituitary gland and ovaries.** Olafson RP, O'Steen WK. To determine whether the absence of pituitary or ovarian hormones would influence retinal degeneration, female albino rats were either hypophysectomized (HYPEX) or ovariectomized (OVEX) before pubery. Later, they were exposed to continuous light for periods up to 45 days. Retinas evaluated by light microscopic measurements showed damage to the outer nuclear layer (ONL) and photoreceptor layer in both the operated and intact, control rats. However, the degree of damage observed in retinas of HYPEX and OVEX rats was significantly less than that observed in retinas of intact rats exposed to the same lighting conditions. Therefore, hypophysectomy and ovariectomy, which influence the normal development of sexual maturation when performed on immature rats, significantly reduce photoreceptor damage in adult rats exposed to continuous light.

Invest Ophthalmol Vis Sci 1996 Oct;37(11):2243-57. **Retinal light damage in rats with altered levels of rod outer segment docosahexaenoate. Organisciak DT, Darrow RM, Jiang YL, Blanks JC.** PURPOSE: To compare retinal light damage in rats with either normal or reduced levels of rod outer segment (ROS) docosahexaenoic acid. METHODS: Weanling male albino rats were maintained in a weak cyclic light

environment and fed either a nonpurified control diet or a purified diet deficient in the linolenic acid precursor of docosahexaenoic acid (DHA). Half the rats on the deficient diet were given linseed oil, containing more than 50 mol% linolenic acid, once a week to maintain ROS DHA at near normal levels. Diets and linseed oil supplementation were continued for 7 to 12 weeks. To replenish DHA in their ROS, some 10-week-old rats on the deficient diet were given linseed oil three times a week for up to 3 additional weeks. Groups of animals were killed at various times for ROS fatty acid determinations or were exposed to intense green light using intermittent or hyperthermic light treatments. The extent of retinal light damage was determined biochemically by rhodopsin or photoreceptor cell DNA measurements 2 weeks after exposure and morphologically by light and electron microscopy at various times after light treatment. RESULTS: **Rats maintained for 7 to 12 weeks on the linolenic acid-deficient diet had significantly lower levels of DHA** and significantly higher levels of n-6 docosapentaenoic acid (22:5n-6) in their ROS than deficient-diet animals supplemented once a week with linseed oil or those fed the nonpurified control diet. As determined by rhodopsin levels and photoreceptor cell DNA measurements, deficient diet rats **exhibited protection against retinal damage from either intermittent or hyperthermic light exposure. However, the unsaturated fatty acid content of ROS** from all three dietary groups was the same and greater than 60 mol%. In 10 week-old deficient-diet rats given linseed oil three times a week, ROS DHA was unchanged for the first 10 days, whereas 22:5n-6 levels declined by 50%. After 3 weeks of treatment with linseed oil, ROS DHA and 22:5n-6 were nearly the same as in rats supplemented with linseed oil from weaning. The time course of susceptibility to retinal light damage, however, was different. Hyperthermic light damage in rats given linseed oil for only 2 days was the same as for rats always fed the deficient diet. Six days after the start of linseed oil treatment, retinal light damage was the same as in rats given the linseed oil supplement from weaning. Morphologic alterations in ROS of linseed oil-supplemented rats immediately after intermittent light exposure were more extensive than in either the deficient-diet animals or those fed the control diet. The deficient-diet rats also exhibited better preservation of photoreceptor cell nuclei and structure 2 weeks after exposure. CONCLUSIONS: Rats fed a diet deficient in the linolenic acid precursor of DHA are protected against experimental retinal light damage. The relationship between retinal light damage and ROS lipids does not depend on the total unsaturated fatty acid content of ROS; the damage appears to be related to the relative levels of DHA and 22:5n-6.

Exp Neurol 1970 May;27(2):194-205. **Retinal and optic nerve serotonin and retinal degeneration as influenced by photoperiod.** O'Steen WK.

Invest Ophthalmol Vis Sci 1982 Jan;22(1):1-7. **Antagonistic effects of adrenalectomy and ether/surgical stress on light-induced photoreceptor damage.** O'Steen WK, Donnelly JE. Light-induced damage to retinal photoreceptors in influenced by the endocrine status of the animal during the period of exposure. Experimental manipulation of the pituitary gland and of prolactin levels has been shown to affect retinal damage in rats exposed to visible light. When rats are experimentally stressed, prolactin secretion from the pituitary gland occurs as does secretion of adrenocorticotropic hormone (ACTH), which stimulates the release of adrenal cortical hormones. Since prolactin appears to influence retinal damage and since stressed animals have increased serum levels of prolactin, a comparison of photoreceptor damage in animals in which the adrenal glands were removed or which had been experimentally stressed was undertaken in this study. Adrenalectomized rats had thicker outer nuclear layer (ONL) measurements than those found in sham-operated animals. Stressed rats had severely damaged retinas with cystic degeneration and significantly reduced ONL thickness measurements as compared to retinas of unstressed and adrenalectomized rats. **Therefore hormones of the pituitary-adrenal system appear to be involved in the damage to the retina by light, and this response may be related to an interaction or synergism between the adrenal gland, stress, and prolactin secretion.**

Brain Res 1990 Nov 26;534(1-2):99-105. **Water deprivation protects photoreceptors against light damage.** O'Steen WK, Bare DJ, Tytell M, Morris M, Gower DJ. "Photoreceptor cell death after light-damage and during aging in rats is associated with the hormonal status of the animal, as well as other environmental and intrinsic factors. Restricted caloric intake extends the life of rodents and is usually accompanied by a reduction in water consumption. In this study, male and female rats were placed on restricted water intake for either 3 or 7 days to induce dehydration." "Photoreceptor cells of 7-day, dehydrated male and female rats survived light-damage significantly better than those allowed water ad libitum; however, after 3 days of water restriction, only the male rats demonstrated protection from photodamage." "AVP increased by 350% during the 7-day period of dehydration. Protection of photoreceptors from light-damage in this study may be correlated with osmotically stimulated changes in the retinas of dehydrated animals."

Brain Res 1985 Oct 7;344(2):231-9. **Neuronal damage in the rat retina after chronic stress.** O'Steen WK, Brodish A. Long-term exposure to escapable foot shock has been used to determine if chronic stress influences neuronal cell death in the retina of albino and pigmented rats. Histopathologic and morphometric approaches analyzed changes in photoreceptors and neurons of the bipolar and ganglion cell layers of the retina. Albino Fischer rats when exposed to chronic stress for 4-8 h daily for 1 week to 6 months, developed severe retinal damage, as compared to unstressed control retinas, with reduction in photoreceptor and bipolar neurons, particularly in the superior central retina. The damage was observed in male and female rats, but males appeared to be more susceptible to the influence of stress than female animals. Ganglion cells were unaffected. Photoreceptor destruction did not occur in Long-Evans pigmented rats under identical experimental conditions. The results suggest that: **input of the sensory stimulus, light, to the retina of stressed rats augmented neuronal damage and might be required for its initiation;** and hormones and/or neurotransmitters associated with long-term chronic stress might be related to increased neuronal cell death in the mammalian retina.

Invest Ophthalmol Vis Sci 1977 Oct;16(10):940-6. **Effects of hypophysectomy, pituitary gland homogenates and transplants, and prolactin on photoreceptor destruction.** O'Steen WK, Kraeer SL. "Prepubertal removal of the pituitary gland, which in young animals influences sexual maturation, reduces significantly the amount of retinal photoreceptor destruction when the rats are exposed to continuous illumination in adulthood. When crude pituitary gland homogenate is administered to adult rats hypophysectomized prior to puberty, photoreceptor destruction is more severe. Transplantation of whole pituitary glands to the kidney capsule of hypophysectomized rats also reduces the effect of pituitary gland removal and results in more extensive damage to receptor cells than found in hypophysectomized, adult animals. **Hypophysectomized rats treated with prolactin had more severe retinal damage than untreated, hypophysectomized rats."** "Results of these studies indicate the hormones of the pituitary gland have a regulatory influence on the severity of light-induced, retinal photoreceptor damage in the rat."

Life Sci 1985 Nov 4;37(18):1743-6. **Stress-induced synthesis of melatonin: possible involvement of the endogenous monoamine oxidase inhibitor (tribulin).** Oxenkrug GF, McIntyre IM.

Mech Ageing Dev 2000 Jan 10;112(3):169-83. **Double bond content of phospholipids and lipid peroxidation negatively correlate with maximum longevity in the heart of mammals.** Pamplona R, Portero-Otin M, Ruiz C, Gredilla R, Herrero A, Barja G.

Prostaglandins Leukot Essent Fatty Acids 2001 Feb;64(2):75-80. **Comparative studies on lipid peroxidation of microsomes and mitochondria obtained from different rat tissues: effect of retinyl palmitate.** Piergiacomi VA, Palacios A, Catala A.

Curr Eye Res 1992 Oct;11(10):939-53. **Oxygen-induced retinopathy in the rat: hemorrhages and dysplasias may lead to retinal detachment.** Penn JS, Tolman BL, Lowery LA, Koutz CA.

Vision Res 1995 May;35(9):1247-64. **Studies on the role of the retinal dopamine/melatonin system in experimental refractive errors in chickens.** Schaeffel F, Bartmann M, Hagel G. Zrenner E.

Exp Clin Endocrinol Diabetes 1997;105(2): 109-12. **Melatonin and serotonin regulate the release of insulin-like growth factor-I, oxytocin and progesterone by cultured human granulosa cells.** Schaeffer HJ, Sirotkin AV.

Zh Evol Biokhim Fiziol 1989 Jan-Feb;25(1):52-9. **[Seasonal characteristics of the functioning of the hypophysis-gonad system in the suslik** Citellus parryi] Shvareva NV, Nevretdinova ZG. "In females, FSH was found in the blood in October, being absent from November to **January; beginning from February, it may be found both in sleeping and active** animals." **"Estradiol secretion was noted in hibernating females, whereas progesterone was found in the blood only in May."**

J Pineal Res 1985;2(1):39-49. **Melatonin and N-acetylserotonin stress responses: effects of type of stimulation and housing conditions.** Seggie J, Campbell L, Brown GM, Grota LJ.

Acta Ophthalmol Scand 2001 Aug;79(4):428-30. **Presumed sertraline maculopathy.** Sener EC, Kiratli H.

Paediatr Perinat Epidemiol 1999 Apr;13(2):128-30. **Effects of premature exposure to light: a credibility struggle.** Silverman WA.

J Pineal Res 1994 Oct;17(3):112-7. **Direct influence of melatonin on steroid, nonapeptide hormones, and cyclic nucleotide secretion by granulosa cells isolated from porcine ovaries.** Sirotkin AV. **"It was found that melatonin is able to inhibit progesterone and stimulate estradiol secretion."** "The present observations suggest a direct effect of melatonin on the steroid, nonapeptide hormone, and cyclic nucleotide release from porcine ovarian cells."

J Pineal Res 1994 Oct;17(3):112-7. **Direct influence of melatonin on steroid, nonapeptide hormones, and cyclic nucleotide secretion by granulosa cells isolated from porcine ovaries.** Sirotkin AV.

Prog Clin Biol Res 1989;312:229-49. **Inhibitors of the arachidonic acid cascade in the management of ocular inflammation.** Srinivasan BD, Kulkarni PS.

J Nutr 2000 Dec;130(12):3028-33. **Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils.** Song JH, Fujimoto K, Miyazawa T. **"Thus, high incorporation of (n-3) fatty acids (mainly DHA) into plasma and tissue lipids due to DHA-containing oil ingestion may undesirably affect tissues by enhancing** susceptibility of membranes to lipid peroxidation and by disrupting the antioxidant system."

Acta Ophthalmol (Copenh) 1992 Feb;70(1):115-22. **Effects of steady electric fields on human retinal pigment epithelial cell orientation and migration in culture.** Sulik GL, Soong HK, Chang PC, Parkinson WC, Elner SG, Elner VM

Ned Tijdschr Geneeskd 2001 Dec 29;145(52):2521-5. **[Administration of glucocorticosteroids to premature infants: increasing evidence of adverse effects]** [Article in Dutch] van Bel F. **"Neonatal glucocorticosteroid therapy is increasingly being used for the prevention of chronic lung disease in very premature infants. In the short term this therapy is usually successful. There is, however, increasing evidence for long-term adverse effects. In particular there seems to be an increased chance of abnormal brain development, which later results in locomotory dysfunction, developmental delay and cerebral palsy."**

Brain Res 1984 Feb 27;294(1):166-8. **Pineal methoxyindoles depress calcium uptake by rat brain synaptosomes.** Vacas MI, Keller Sarmiento MI, Cardinali DP.

Ann N Y Acad Sci 1994 Nov 17;738:408-18. **Serotonin binding proteins: an in vitro model system for monoamine-related neurotoxicity.** Vauquelin G, Del Rio MJ, Pardo CV.

J Hypertens Suppl 1985 Dec;3 Suppl 3:S107-9. **Seasonal variation in the development of stress-induced systolic hypertension in the rat.** Weinstock M, Blotnick S, Segal M. "Seasonal variation in blood pressure in human hypertensives prompted us to investigate whether such a phenomenon also occurs in rats made hypertensive by environmental stress." **"Systolic pressure increased by 14-25 mmHg after 6-8 weeks of stress from October to January. Artificial environmental light for 15 h prevented development of hypertension by stress,** which could also be reversed by acute administration of propranolol." "Hypertensive rats had significantly greater relative heart and adrenal weights. This phenomenon can be explained by amplification of **sympathetic pressor activity by stress hormones, adrenaline, corticosterone and prolactin, under the influence of melatonin."**

Invest Ophthalmol Vis Sci 1992 May;33(6):1894-902. **Melatonin increases photoreceptor susceptibility to light-induced damage.** Wiechmann AF, O'Steen WK. **"Pinealectomy has been shown to protect photoreceptors from light-induced damage, and melatonin treatment has been reported to increase the degree of photoreceptor damage in albino rats."** "The animals that received daily melatonin injections (100 micrograms) in the late afternoon (3 hr before lights off) for 1-3 days before photodamage showed an approximate 30% greater reduction compared with sham control animals in ONL thickness in the superior quadrant, the area most susceptible to light damage. Melatonin injections given after the photodamage did not affect ONL thickness. Although retinal susceptibility to light damage varied with time of day, the degree to which melatonin increased the degree of damage appeared unaffected by the time of day. These results suggest that melatonin may be involved in some aspects of photoreceptor sensitivity to light damage."

J Neurochem 1986 Oct;47(4):1181-9. **Effects of arachidonic acid on glutamate and gamma-aminobutyric acid uptake in primary cultures of rat cerebral cortical astrocytes and neurons.** Yu AC, Chan PH, Fishman RA.

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Ray Peat's Newsletter

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Folly is the cloke of knavery

Leakiness, aging, and cancer

A thin layer of fibrin lining blood vessels provides a filtering barrier that helps to strengthen the wall and prevent other proteins from leaking out of the vessels, and it participates in repair processes when the blood vessel is broken.

Cellular energy metabolism is the basis for maintaining the barrier functions. Energy depletion causes the endothelial cells lining blood vessels to become excessively permeable.

When the organism's resistance is low, proteins and fats that normally remain inside the bloodstream can escape into the extracellular matrix and enter cells, contributing to their stress and disorganization, and other materials can escape from cells and enter the bloodstream.

One of the simplest demonstrations of fibrin leakage is to shine a beam of light into the eye; the presence of fibrin and other inappropriate molecules diffuses the light, causing a "flare" in the aqueous compartment (Sawa, 1990). Albumin, a small protein from the blood, is often seen in the urine during stress. The effects of that sort of leakage vary with each organ.

Fibrin is an essential structural and functional part of the organism, but when it escapes from the bloodstream it participates in the degenerative processes of inflammation, fibrosis, and tumor formation. (Its fragments stimulate secretion of inflammatory mediators: Hamaguchi et al., 1991.)

In the hormonal environment dominated by estrogen, mild stresses such as exertion, or even restless sleep, allow toxins (and sometimes bacteria) from the intestine to enter the bloodstream, triggering a complex chain of events that create a systemic inflammatory state. Although these processes have been observed in many simple experiments, their implications are almost always neglected or denied or explained away.

Incorporation of certain polyunsaturated fats into the tissues increases the leakiness of blood vessels, and amplifies the reactions to stresses and inflammatory stimuli.

Antioxidants, thyroid hormone, progesterone, and antiinflammatory agents, including glycine or gelatin, niacin, and saturated fats, can prevent, and in many cases reverse, these degenerative inflammatory processes.

Even a single celled organism has to keep its parts separate, and highly differentiated multicelled organisms have many special systems that serve to keep their parts separate, so the different tissues and organs can maintain their distinct functions.

The movement of substances from blood to cell, and from cell to cell, is normally very tightly controlled, and when the systems that control those movements of water and its solutes are damaged, the tissues' structures and functions are altered. The prevention of inappropriate leakiness can protect against the degenerative processes, and against aging itself, which is, among other things, a state of generalized leakiness.

When cells' energy is depleted, water and various dissolved molecules are allowed to move into the cells, out of the cells, and through or around cells inappropriately. The weakened cells can even permit whole bacteria and similar particles to pass into and out of the blood stream more easily.

One of the earliest investigators of the effects of stress and fatigue on nerves and other cells was A.P. Nasonov, in the first half of the 20th century. A.S. Troshin (1956) has reviewed his work in detail. He showed that in cells as different as algae and nerve cells, fatigue caused them to take up dyes, and that the dyes were extruded, if the cells were able to recover their energy. When nerve cells are excited for a fraction of a second, they take up sodium and calcium, but quickly eliminate them. Prolonged excitation, leading to fatigue, can gradually shift the balance, allowing more substances to enter, and to stay longer.

When nerves or other cells are quickly killed with heavy metals such as osmium, the metals are visible in a layer at the surface, which is sometimes taken as evidence of a "cytoplasmic membrane," but if the cells have suffered oxygen deprivation or have been injured by X-rays, the

metal will be visible as a grey color evenly distributed through the cell. The deposition of the metal occurs when it reacts with electrons. In the relatively vital cell, the heavy metal stops at the surface, and is mostly reduced there, but the devitalized cell presents no structural or chemical barrier to the entry of the metal, and the reactive electrons appear to be evenly distributed through the cell. Oxygen deprivation, X-irradiation, and other stresses cause the cell to be unable to use electrons to produce energy, and instead the electrons are available to react destructively with whatever may be available. While Nasonov showed that dyes and even particles enter energetically depleted cells. newer techniques are able to show that the leaky cells are structurally disrupted by the excessive reduction of their proteins, by excited electrons and free radicals.

In the 1970s, experimenters found that muscles from vitamin E deficient animals released their enzymes when washed in a saline solution, more easily than did the muscles from vitamin E replete animals. Other experiments around the same time showed that reducing the ATP of muscles caused a similar loss of their ability to retain their proteins.

Over the years, many experiments have established. both in vitro and in vivo. that fatigue, stress, aging, and inflammation cause cells to lose their normal constituents, but also to allow foreign materials to enter more easily.

When I was working on my thesis, around 1970, investigating the effects of aging on the metabolism of the uterus, I found that the changes occuring during aging were (in all the ways I tested) the same as those produced by X-irradiation, excess estrogen, oxygen deprivation, excess polyunsaturated fats, and vitamin E deficiency.

Although everyone working in the lab was familiar with the appearance of the uterus from old hamsters (they are typically large, stiff, and somewhat bluish or purplish), everyone was surprised when I suggested that the aged uteri seemed to function as if they were under the influence of a considerable amount of estrogen. Everyone was familiar with the medical textbook doctrine that "menopause is caused by estrogen deficiency." In humans, gynecologists know about "Chadwick's sign," the fact that the uterine cervix turns blue or purple during pregnancy, and everyone knows that blood is blue when it's deprived of oxygen, so it's surprising that estrogen's effect on tissue oxygenation isn't widely recognized.

When estrogen is given to an animal, it almost instantly causes capillaries to become leaky, allowing water to move out of the blood stream, and at the same time, estrogen causes cells to take up water. Both of these processes are the same as the early effects of oxygen deprivation. In the normal reproductive cycle, the surge of estrogen lasts only a few hours, and normal permeability is quickly restored by increasing progesterone. During those intermittent short exposures to estrogen, there isn't usually a massive leakage of serum proteins into the tissues. During the time of estrogenic influence, all kinds of cells are influenced, with the excitatory equilibrium of nerve cells, glandular cells, and immune system cells being shifted, lowering the threshold of excitation, or prolonging the excited state.

Anything that causes inflammation causes a similar loss of water from the blood, as it is taken up by swelling cells. If inflammation is generalized, it causes circulatory shock, because the volume of the blood has become insufficient to serve the organism's needs. One of Hans Selye's earliest observations of the effect of an overdose of estrogen was that it causes shock.

Although water loss causes the blood to become more viscous under the influence of estrogen, the plasma becomes hypotonic, meaning that it contains fewer osmotically active solutes than normal; some of the sodium that helps to maintain the blood's osmotic balance is lost through the kidneys, and some is taken up by the red blood cells and other cells. The osmotic imbalance of the blood causes tissue cells to take up more water, contributing to their increased excitability. In many cases, the vascular leakage of inflammation and shock can be corrected by using osmotically active substances, such as starch solutions, gelatin, or concentrated sodium chloride.

The tissue water retention caused by estrogen, hypoxia, and stress is analogous to the swelling of gels and colloids, that is, it's governed by the state

of the electrons and counter-ions in the system. Excitation, fatigue, or injury can cause a shift of pH toward alkalinity, causing water uptake and swelling.

The blue color of the pregnant cervix, or of the uterus in an animal given an overdose of estrogen, indicates that the tissue isn't sufficiently oxygenated to maintain its normal red color, even though the flow of blood is increased. Some experimenters have noticed that newborn animals sometimes have the postural reflex (lordosis) that indicates an estrogenic state, and that suffocation can produce the same reflex. Irradiating animals with x-rays will also produce the whole range of estrogenic effects.

One of the features of the aged uterus that I studied was the age pigment, lipofuscin, a brown waxy material that accumulates in old or stressed tissues. Prolonged dosage with estrogen accelerates the formation of this pigment, which is largely derived from oxidized polyunsaturated fatty acids. Increased amounts of those fats in the diet, or a deficiency of vitamin E, or exposure to ionizing radiation, or oxygen deprivation, can also accelerate the formation of the age pigment. The presence of the pigment intensifies the effect of estrogen, since the pigment wastes oxygen by functioning as an oxidase enzyme.

Other tests that I did on aged, or estrogenized, uterine tissue indicated that several oxidative systems were activated; for example, the tissues showed an extremely high activity of the enzyme peroxidase, and a very intense reduction of a chemical dye (tetrazolium/formazan) that indicates the presence of reductive and oxidative activity, of the sorts caused by radiation and oxygen deprivation. These reductive and oxidative processes include the production of some free radicals that are capable of reacting randomly with polyunsaturated fatty acids.

The interactions between estrogen and the polyunsaturated fats are now coming to be more widely recognized as important factors in the inflammatory/hyperpermeable conditions that contribute to the development of heart and blood vessel disease, hypertension, cancer, autoimmune diseases, dementia, and other less common degenerative conditions.

Estrogen increases lipid peroxidation, and maintains a chronically high circulating level of free fatty acids, mainly PUFA, activates the phospholipases that release arachidonic acid from cells leading to formation of prostaglandins and isoprostanes, and increases the enzymes that form the inflammation-promoting platelet activating factor (PAF) while suppressing the enzymes that destroy it, and increases a broad range of other inflammatory mediators, interleukins, and NF-kappa B.

The leakage of enzymes out of cells and into the blood stream is recognized medically as evidence of damage to the organ that is losing them. Different combinations of enzymes are commonly considered to be evidence of a heart attack, or skeletal muscle damage, or liver disease, pancreatitis, prostate cancer, etc. But often the reason for the leakage isn't understood. Hypothyroidism, for example, causes leakage of enzymes, possibly mainly from the liver, but also from other organs. Excess estrogen, intense exercise, starvation, anything that increases lipid peroxidation and free radical production, such as drinking alcohol when the tissues contain polyunsaturated fats, can cause organs such as heart and liver to leak their components.

The loss of enzymes increases the energy needed to stay alive, but it doesn't necessarily change the basic functions of the cell. (Though when mitochondrial enzymes leak out into the cytoplasm, the cell's energy metabolism is impaired, at least temporarily.) But the entry of catalytic materials from other tissues changes the organization of a cell, giving it conflicting instructions. In many situations, as L.V. Polezhaev and V. Filatov demonstrated, the substances released during stress and degeneration serve to stimulate healing and regeneration. But when the resources aren't available for full repair or regeneration, only a scar, or atrophic fibrosis, or a tumor will be formed.

In severe stress, intracellular fibrin deposits have been found in the heart (Buja, et al., 1976) and other organs, including the prostate gland. Deficiency of testosterone causes vascular leakage into the prostate. Fibrin promotes tumor growth, partly by serving as a matrix, partly by releasing

stimulatory peptides. Estrogen and prolactin contribute to the edema of the prostate resulting from the absence of testosterone.

Kidney disease, diabetes, pregnancy toxemia and retinal degeneration are probably the best known problems involving vascular leakage, but increasingly, cancer and heart disease are being recognized as consequences of prolonged permeability defects. Congestive heart failure and pulmonary hypertension commonly cause leakage of fluid into the lungs, and shock of any sort causes the lung to get "wet," a waterlogged condition called "shock lung." Simply hyperventilating for a couple of minutes will increase leakage from the blood into the lungs; hyperventilation decreases carbon dioxide, and increases serotonin and histamine. Hyperoxia itself contributes to lung injury, and exacerbates emphysema, though it is common to see patients breathing a high concentration of oxygen. Emphysema (which can be caused by hypothyroidism or hyper-estrogenism, and often can be cured by thyroid or progesterone) and many other respiratory problems are associated with capillary leakage. Cells of the lung and intestine are able to synthesize their own fibrin, apparently because of their special problems in preventing leakage. Prolonged systemic inflammation can lead to lung fibrosis, and fibrosis increases the likelihood of lung cancer.

The inflammatory state that causes exaggerated cellular permeability is very closely related to "hyperventilation," the loss of too much carbon dioxide. The release of serotonin during hyperventilation isn't the only cause of vascular leakage; the carbon dioxide itself is an essential factor in regulating the state of cellular electrons and in maintaining cellular integrity. Hyperventilation, like the shift from oxidative to glycolytic energy production that typifies estrogenized or stressed cells or cancer, raises intracellular pH. In the case of mast cells, increasing alkalinity causes them to release histamine (Alfonso, et al., 2005), but similar "alkaline-induced exocytosis" seems to occur in all stressed tissues.

Since histamine is formed by decarboxylation of histidine, the presence of carbon dioxide in a cell would tend to restrain the reaction, by mass action. All types of cell, at least in animals, form histamine as they are being killed. Sensory nerves in the carotid body respond to hypoxia in the artery supplying the brain by sending signals that accelerate breathing; recent information suggests that it is the formation of histamine in the carotid body that responds to oxygen deprivation (Koerner, et al., 2003). When the formation of histamine is inhibited by blocking histidine decarboxylase, it can slow the rate of breathing (Izumizaki, et al., 2000).

The blood platelets that become incontinent and leak serotonin in the absence of carbon dioxide are undergoing the same structural stresses experienced by endothelial cells, smooth muscle cells, mast cells and all other cells when carbon dioxide is depleted. Although it has been about 70 years since Yandell Henderson made it clear that supplemental oxygen should be combined with carbon dioxide, mechanical ventilation in hospitals is still causing lung injury resulting from hyperventilation, i.e., the absence of carbon dioxide.

A similar misunderstanding of biology was involved in the use of dialysis to treat kidney disease. Until recently, commercial dialysis fluids contained acetate and/or racemic lactate instead of bicarbonate, because of the difficulty of preparing bicarbonate solutions, and the result was that very prolonged dialysis would damage the brain and other organs. (Veech and Gitomer, 1988, Veech and Fowler, 1987.) Dialysis has been seen to increase lung permeability (Bell, et al., 1988).

Amyloidosis produced by chronic dialysis affects all organs, but its effects are best known in the brain, heart, kidneys, and lungs. Serum amyloid-A is one of the acute phase proteins, like C-reactive protein (CRP), that are produced by inflammation. Estrogen, radiation and other stresses increase those pro-inflammatory acute phase proteins, and decrease protective albumin, which is called a "negative acute phase protein," since it decreases when the other acute phase proteins increase. The liver is the major source of the acute phase proteins, and it is constantly burdened by toxins absorbed from the bowel; disinfection of the bowel is known to accelerate recovery from stress.

Seen from the perspective of the stress-leakage syndrome, any serious injury or sickness damages all organs.

The exhaled breath is being used to diagnose inflammatory lung disease, since so many of the mediators of inflammation are volatile, but systemic diseases such as cancer and arthritis, and relatively minor stress can be detected by changes in the chemicals found in the breath. Polyunsaturated fats and their breakdown products--aldehydes, prostaglandins, isoprostanes, hydrocarbons, and free radicals--and carbon monoxide, nitric oxide, nitrite, and hydrogen peroxide are increased in the breath by most stresses.

Both proline and glycine (which are major amino acids in gelatin) are very protective for the liver, increasing albumin, and stopping oxidative damage.

Saturated fats are protective against free radical damage and can reverse liver fibrosis.

Thyroid hormone protects against excess estrogen, and can prevent or reverse fibrosis of the heart (Yao, et al., 1992). It's the main regulator of energy production and tissue integrity.

Antiestrogens are widely effective against vascular leakage. Thyroid, progesterone, and testosterone are among the most effective natural antiestrogens, and they are curative in many conditions that involve vascular leakage. Progesterone and pregnenolone have been called the antifibromatic steroids, and progesterone has been used to treat many inflammatory and fibrotic diseases, including cancer.

The antiserotonin drugs are being increasingly used to treat fibrotic diseases, and other problems related to vascular leakage. The antiserotonin drugs lower prolactin secretion, and prolactin is closely associated with estrogen in causing vascular leakage. Vitamin D, magnesium, and calcium (Graham, et al., 1990; Chen and Ruan, 1995; Chen et al., 1994) can reduce capillary permeability, possibly by reducing parathyroid hormone and mast cell products including serotonin.

Antiinflammatory and anticoagulant things, especially aspirin and vitamin E, protect against the accelerated turnover of fibrinogen/fibrin caused by estrogen and the various inflammatory states.

Since polyunsaturated fatty acids become integrated into all types of cell, and cause so many types of damage when they are released, everything which inhibits their release is protective. Niacinamide, Benadryl, aspirin (Yu, et al., 2003), and procaine help to reduce the release of free fatty acids. Although many studies have demonstrated antiaging, antiinflammatory, and anticancer effects of procaine, its therapeutic use has never been widely accepted, because it didn't fit into traditional ideas of "rational drug therapy." It normalized too many systems to seem "rational." Since people and animals clearly felt better when they were given procaine, an attempt was made to ascribe its action to its slight stimulating action as an inhibitor of MAO, but its main actions probably include antihistamine and anticholinergic effects and inhibition of phospholipases and other lipolytic enzymes (e.g., Chen, et la., 2002; D'Costa and Angel, 1975). Belladonna and atropine have some of those same antiinflammatory effects.

Although fish oil interferes with prostaglandin synthesis, it can contribute to the formation of PAF (Triggiani, et al., 1990), and other mediators of inflammation, energy suppression, and free radicals, including nitric oxide (Nishimura, et al., 2000; Hirafuji, et al., 2002). Since the fish oils are commonly studied by comparing the supplemented animals with "control" animals receiving soy oil, corn oil, or safflower oil, which are strongly pro-inflammatory and broadly toxic, it isn't surprising that their effects usually seem favorable. But when they are compared with saturated fats (as I mentioned in the "Fats and degeneration" newsletter) or with a fat free diet, their effects are seen to be pro-inflammatory and toxic.

Adrenaline, like estrogen, increases lipolysis and free fatty acids in the bloodstream, so keeping adrenaline low most of the time (especially at night) helps to minimize inflammation and vascular leakiness. Hypothyroidism, and the associated hypoglycemia, contribute to the formation of adrenaline, and the thyroid stimulating hormone itself, even if thyroxine and T3 seem normal, can contribute to production of the major

inflammatory mediators. Antihistamines help to prevent excessive adrenaline action.

Although caffeine, if it's combined with hypoglycemia and stress, will increase lipolysis and free fatty acids, several of the methylxanthines, including caffeine, theophylline, and pentoxifylline, can protect against capillary leakage, probably by a variety of antiinflammatory actions, including inhibition of nitric oxide synthesis (Bereta, et al., 1994).

In general, the effects are better when several of the protective agents are used together, since they protect against leakage by many different mechanisms.

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Finally, the Lendrum-Fraser histochemical procedure used to identify fibrin leakage in tissues with vascular damage was applied to sections of the ventral prostate gland. This stain revealed diffuse fibrin accumulation in periglandular areas outside the capillaries and blood vessels in prostates from 24-h castrated rats, but not in prostates of sham-operated rats. Our results confirm an early effect of castration on the vascular system of the rat ventral prostate identified by increased apoptosis of endothelial cells and vascular leakiness. As these changes temporally precede the loss of epithelial cells, we propose that they may be causal rather than incidental to regression of the rat ventral prostate after castration.

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Ray Peat's Newsletter

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Thyroiditis. Some confusions and causes of "autoimmune diseases"

Girls' thyroid glands usually enlarge during puberty, and in pregnancy it's entirely normal for the gland to enlarge and to become more active. Eighty years ago, when iodine deficiency was more common in the US and Europe, the idea of a "colloid goiter" was common. In certain regions, many people had enlarged thyroids that contained a large amount of colloid--colloid is the viscous protein (thyroglobulin) solution formed in tiny compartments in the thyroid gland, which can be broken down by "digestive" (proteolytic) enzymes of the cells that have secreted it, forming the thyroid hormones, and allowing them to be released into the blood stream. The hormones are formed as the accumulated protein is broken down; the hormone itself isn't stored in the gland.

The reason for the enlargement of the gland during puberty and in pregnancy, and during some kinds of stress, is that the colloid is formed faster than it is digested by the thyroid gland and secreted into the blood. If something, such as an excess of estrogen, is blocking the production of the thyroid hormone, the gland is likely to enlarge, because the pituitary secretes more thyroid stimulating hormone (TSH) when there is a deficiency of thyroid hormone.

In vitro experiments show that estrogen activates the formation of the colloid, but inhibits its breakdown into the hormones. Progesterone, on the other hand, activates the process of proteolytic digestion and so increases the release of hormones from the gland, decreasing the accumulation of the colloid.

Therefore, when progesterone is deficient or estrogen is present in excess, the colloid tends to accumulate (even to the point of causing a visible enlargement of the gland, a "colloid goiter"), at the same time that the person may be hypothyroid, because the hormone isn't being released from the stored colloid, into the blood stream. But, largely because no one wants to suggest that estrogen can

Injury to the thyroid apparently precedes the development of "autoimmune thyroiditis." There is evidence that tissue injury precedes the appearance of "autoantibodies" in other conditions, too.

Many people with metabolic problems, including hypothyroidism, are being told that they have "a genetic disease." This belief encourages both physicians and their customers to commit themselves to inappropriate treatments, and to misinterpret the results of tests.

Eating seaweed or other foods or supplements containing iodine can cause both hypothyroidism and thyroiditis. The iodate sometimes used as an oxidizing agent in breads have probably contributed to thyroid disease in the industrialized countries.

Dental x-rays, which can cause cancer of the thyroid, brain, and eye, certainly have increased the incidence of thyroiditis and hypothyroidism. The radioactive isotopes that are often foolishly used for supposedly "diagnostic" purposes probably contribute to the incidence and severity of hypothyroidism and thyroiditis.

Besides iodine, radioactive isotopes, and x-rays, other environmental toxins, including mercury and dioxins can cause thyroiditis, but diet and estrogens are probably the causes of most thyroid problems.

A generalized inflammatory state, rather than specific "autoimmunity," is responsible for thyroiditis and other "autoimmune degenerative" diseases.

A "respiratory defect" is behind the inflammatory condition.

Correcting a thyroid deficiency tends to gradually normalize the antibodies.

be pathogenic, an enlarged thyroid gland is now likely to be diagnosed as "Hashimoto's thyroiditis" (or Hashimoto's struma, or goiter, or disease).

Hashimoto's disease is clearly defined as the infiltration of the gland with lymphocytes, "causing destruction" of the gland's active tissue and leading to hypothyroidism. The only way to know that the gland is being invaded by large numbers of lymphocytes is by biopsy, but the condition is normally diagnosed by pure guesswork, without any biopsy. Sometimes "antithyroid antibodies" found in the blood are used to diagnose Hashimoto's disease, but the presence of those antibodies in the blood doesn't mean that they originated in the thyroid gland, and even though they have very specific names (e.g., "antithyroglobulin," "antithyroperoxidase") related to the thyroid gland, they aren't even specific for the thyroid gland. It has been suggested that similarities in molecular structure between thyroglobulin and connective tissue proteins could account for the finding of "antithyroid antibodies" **more frequently in rheumatoid arthritis and Sjogren's syndrome than in Hashimoto's disease and Graves' disease** (Ruggeri, et al, 2002).

In the last 60 years, most of estrogen's toxic effects have been hushed up by the drug industry, and estrogen's central antirespiratory and antithyroid actions are unknown to most contemporary endocrinologists. But endocrinologists often do know that estrogen causes the thymus gland to atrophy, and that the thymus gland is intimately involved in maintaining normal immune functions.

The degenerating thymus gland undergoes invasion by lymphocytes and the replacement of active tissue by fibrous tissue, under the influence of estrogen or stress. The process of cellular invasion in the thyroid gland probably develops more slowly than that in the thymus, because estrogen's effect on the thymus is very rapid.

The cells that make up the thymus are extremely varied, but a large portion of them are able to phagocytize other cells. This self-phagocytosis probably contributes to the gland's ability to shrink with such great rapidity. When other organs are damaged, the removal of debris can be delayed for days, as phagocytic cells gradually enter the tissues from the blood stream.

Hypothyroidism is an important cause of thymic atrophy, and a thyroid supplement can stimulate regeneration of the thymus.

This correction of the thymic portion of the "immune system" by the thyroid hormone is probably involved in the observation that the "antithyroid" autoantibodies decrease under the influence of supplemental thyroid hormone, but the supplement also affects the thyroid gland, by decreasing the thyroid stimulating hormone, TSH. Excess production of TSH causes an inflammation-like stress, that contributes to the production of the colloid goiter and eventually to disordered structural changes in the thyroid gland. A more efficient production and use of thyroglobulin will decrease the tendency of the overstimulated gland to produce a defective globulin that is antigenic.

So, rather than ignoring the frequency of the simple colloid goiter and calling everything "Hashimoto's autoimmune thyroiditis," if we look at the mechanisms involved in the production of autoantibodies, we will tend to see "thyroiditis" as, usually, the last stage in the development of a simple colloid goiter. The autoantibodies, in a healthy person, are probably part of a corrective repair process, rather than a simply pathogenic factor.

There is an almost obligatory medical genuflection toward "genetic causation" of disease, and especially of thyroid disease, autoimmune disease, and other chronic or degenerative diseases. **The fact that thyroid disease and autoimmune diseases are from five to ten times more frequent in women than in men somehow hasn't increased medical interest in the pathogenic role of estrogen,** and it doesn't prevent platoons of medical researchers from making claims to have discovered "which chromosome carries the disease."

This medical bias means that even the physicians who recognize that hypothyroidism is a condition that should be corrected are not likely to believe that it is important to modify the treatment according to changes in the patient's condition. Many doctors assume that a person never recovers

Part of the problem, Lewontin points out, is the casual way in which geneticists speak. "This is seen even in the naming of genes," he notes. "Geneticists speak casually of the 'gene for white eyes', but of course, there is no such gene. There is a variety of genes whose reading by the cell is proximally involved in the production of eye pigment and its deposition in the eye cells." He points out that genes are said to be "self-replicating," engaged in "gene action", "make" proteins and are "turned on " or "off" by regulatory DNA. "But none of this is true... DNA is among the most inert and non-reactive of organic molecules," he writes. S.W. Samuels, in Genes, Ethics & Environment!, an internet public policy journal.Vol.1, No. 1 October, 2000

from thyroiditis, but the evidence is clear that simply giving supplementary thyroid usually gradually corrects the problem. If other protective measures are taken, recovery will be quicker and more complete. When the diet is optimal, the TSH is likely to be "abnormally low," below 1.0 on the standard scale, even without use of a thyroid supplement. Keeping the level of TSH low contributes to the reduction of the generalized inflammatory state that characterizes hypothyroidism and autoimmunity. TSH should be considered to be one of the stress-related pro-inflammatory anti-respiratory hormones, along with serotonin, histamine, estrogen, parathyroid hormone, and prolactin.

The diet should be relatively free of antithyroid foods, especially legumes and polyunsaturated fats, and the foods of the cabbage family, such as broccoli, should be well cooked, and used no more often than once a week. The polyunsaturated fats interfere with the thyroid hormone, disturb the thymus and other immune functions, and increase the antigenicity of tissues.

A high protein diet, of about 100 grams of good protein daily, is protective, and protein deficiency is a common cause of hypothyroidism. But too much emphasis on the muscle meats, including fish fillets, chicken breast or legs, and the usual steaks and chops, can be antithyroid by providing too much tryptophan. That can be offset by using gelatin liberally (chicken soup and ox-tail soup contain lots of gelatin from the bones and connective tissues), because gelatin contains no tryptophan. Whey, which is sold as a protein supplement, and egg whites contain too much tryptophan, and can be antithyroid if used excessively.

Using large amounts of seaweed can cause hypothyroidism and can injure the thyroid cells, contributing to thyroiditis. Seaweed and other iodine-containing food supplements are often sold to improve thyroid function, but they usually have the opposite effect. An iodine deficiency used to cause goiters in some regions, but in the last 50 years most people in the US and Europe have been getting an excessive amount of iodine.

"We can recall when a TSH of 7.0 or below was considered normal. Years later, the TSH cutoff was 6.4, meaning that anything below that level was considered normal. Still later, the cutoff was moved to 5.5. Now, some labs are reporting a level of 4.2 as being the cutoff level, above which the patient may be hypothyroid." "...at our clinic, a TSH over 3 is considered suspicious...." (p. 75)

"Some doctors prefer the lower limit of a corrected TSH to be 1.0. Others are comfortable with a TSH of 0.5. Some thyroid specialists at the Universtiy of California Medical Center in San Francisco like to see the corrected level around 0.2 (slightly below the normal range of 0.4-5.0). That figure is generally considered by many nonuniversity doctors to be too low, suggesting to them that the patient is on too much thyroid medication.

"At our clinic, we have patients who do not feel well until they take enough medication to lower their TSH level to 0.1." (Page 79) R.L. Shames and K.H. Shames, *Thyroid Power,* 2001.

Endotoxin or other material absorbed from intestinal bacteria contributes to a variety of autoimmune problems, including thyroiditis (Penhale and Young, 1988). Combining an indigestible fiber, such as raw carrot, with mild germicides, such as vinegar and coconut oil, can improve the hormonal environment, while reducing the immunological burden.

Adequate light is another important factor in maintaining a high energy respiratory state and preventing the whole complex of inflammatory, autoimmune, degenerative diseases.

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Science 1985 Oct 18;230(4723):325-7. **Induction of autoimmune thyroiditis in chickens by dietary iodine.** Bagchi N, Brown TR, Urdanivia E, Sundick RS. "In this study, different amounts of potassium iodide were added to the diets of chicken strains known to be genetically susceptible to autoimmune thyroiditis. Administration of iodine during the first 10 weeks of life increased the incidence of the disease...." "Further support for the relation between iodine and autoimmune thyroiditis was provided by an experiment in which iodine-deficient regimens decreased the incidence of thyroid autoantibodies in a highly susceptible strain. These results suggest that excessive consumption of iodine in the United States may be responsible for the increased incidence of autoimmune thyroiditis."

J Ment Defic Res 1991 Dec;35 (Pt 6):512-20. **Effect of thyroid stimulating hormone on adaptive behaviour in Down's syndrome.** Bhaumik S, Collacott RA, Garrick P, Mitchell C. "Both hypothyroidism and Alzheimer's disease may be associated with elevated serum concentrations of thyroid stimulating hormone." "The actual concentrations of thyroid stimulating **hormone were shown to be significantly and inversely correlated with scores of global abilities."**

Clin Endocrinol (Oxf) 1989 Oct;31(4):453-65. **Thyroid autoimmunity in endemic goitre caused by excessive iodine intake.** Boyages SC, Bloot AM, Maberly GF, Eastman CJ, Li M, Qian QD, Liu DR, van der Gaag RD, Drexhage HA. "By interacting with the immune system, iodine excess may trigger the development of autoimmune thyroid disease such as lymphocytic Hashimoto's thyroiditis (LT)." "Affinity chromatographically purified IgG was tested for thyroid growth-stimulating activity (TGI) by two different methods...." "Thyroid growth-stimulating immunoglobulins (TGI) were the major autoantibodies found in children with goitres caused by iodine excess. In the CBA, 12 of 20 (60%) goitrous children and 0 of 12 (0% P less than 0.05) healthy children were positive for TGI." "We conclude that endemic iodine goitre is not associated with Hashimoto's lymphocytic thyroiditis. Nevertheless, autoimmune growth factors such as TGI may play a primary role in the pathogenesis of thyroid growth in this condition."

J Endocrinol Invest 1993 May;16(5):384-91. **Thyroid autoimmunity and female gender.** Chiovato L, Lapi P, Fiore E, Tonacchera M, Pinchera A.

Br J Psychiatry 1987 May;150:674-81. **Characteristic plasma hormone changes in Alzheimer's disease.** Christie JE, Whalley LJ, Bennie J, Dick H, Blackburn IM, Blackwood DH, Fink G. "A systematic endocrine investigation in dementia, depression and control subjects showed that plasma growth hormone (GH) was higher in the morning and **plasma TSH concentrations were higher throughout the day in Alzheimer-type dementia (ATD) than in age-matched depressed patients (MDD), and plasma TSH concentrations were also higher throughout the day in female ATD compared with** age-matched female control subjects. **The increased plasma TSH concentrations could not be due to reduced negative feedback** because plasma T3, T4 and rT3 were in the normal range."

Acta Cytol 1997 Jul-Aug;41(4 Suppl):1369-72. **Aspiration cytology of 131I-induced thyroiditis. A case report.** de la Roza GL, Burke KC, Dumler JS, Aisner SC. "Although 131I may induce morphologic changes similar to those associated with external radiation, a known diagnostic pitfall, the cytology literature on the subject is very sparse. This case exemplifies the thyroid cytologic changes associated with 131I exposure." "Review of the cytologic sample revealed follicular cells with focal, marked cytologic atypia, abundant colloid, stromal fragments, and lymphocytes."

Clin Endocrinol (Oxf) 1991 Jul;35(1):93-6. **Association between autoimmune thyroid disease and familial Alzheimer's disease.** Ewins DL, Rossor MN, Butler J, Roques PK, Mullan MJ, McGregor AM. "This study demonstrates a very high prevalence of autoimmune thyroid disease in Familial Alzheimer's Disease kindreds ...."

J Clin Endocrinol Metab 2002 Apr;87(4):1687-91. **Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations.** Gartner R, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW. "In areas with severe selenium deficiency there is a higher incidence of thyroiditis due to a decreased activity of selenium-dependent glutathione peroxidase activity within thyroid cells. Selenium-dependent enzymes also have several modifying effects on the immune system. Therefore, even mild selenium deficiency may contribute to the development and maintenance of autoimmune thyroid diseases." "We conclude that selenium substitution may improve the inflammatory activity in patients with autoimmune thyroiditis, especially in those with high activity."

Panminerva Med 1996 Mar;38(1):61-3. **Relationship between autoimmune thyroid disease and Alzheimer's disease.** Genovesi G, Paolini P, Marcellini L, Vernillo E, Salvati G, Polidori G, Ricciardi D, de Nuccio I. "As compared to 30 non-demented controls, AD subjects showed a significant increase in the mean values of antithyroglobulin (TgAb) and antimicrosomial (MCSAb) autoantibodies."

J Clin Endocrinol Metab 1996 Mar;81(3):990-4. **Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy.** Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E, Pinchera A. "**Hashimoto's thyroiditis was found in 13.7% of BC patients and in only 2% of the controls** ($P < 0.005$). Other thyroid disorders found in the BC group included 2 cases of Graves' disease, 2 of thyroid carcinoma, and 1 of subacute thyroiditis, whereas in the control group only 1 case of Graves' disease and none of the other disorders were found. Mean free T3, free T4, and TSH concentrations showed no difference between BC patients and controls. The prevalence of thyroperoxidase antibody was higher in BC patients than in controls (23.5% vs. 8%; $P < 0.005$), whereas the prevalence of thyroglobulin antibody was not different. In BC patients the presence of thyroid antibodies was more frequently associated with clinically detectable autoimmune thyroiditis (14 of 26, 51.8%; $P = 0.03$) and was more common in the younger group." "In conclusion, 1) the present study provides evidence that the overall prevalence of thyroid disorders is increased in patients with breast cancer, and 2) thyroid autoimmune disorders, especially Hashimoto's thyroiditis, account to a large extent for the increased prevalence of thyroid disease in patients with breast cancer."

Eur J Cell Biol 1995 Jan;66(1):39-46. **Regulated O-glycosylation of the Alzheimer beta-A4 amyloid precursor protein in thyrocytes.** Graebert KS, Popp GM, Kehle T, Herzog V. **"In thyrocytes, the beta-amyloid precursor protein**

(beta-APP) is expressed, proteolytically cleaved and released into the extracellular space in a TSH-dependent fashion."

Lab Invest 1995 May;72(5):513-23. **Localization and regulated release of Alzheimer amyloid precursor-like protein in thyrocytes.** Graebert KS, Lemansky P, Kehle T, Herzog V. "Dysregulation in the processing of the Alzheimer precursor protein (APP) is thought to be central to the deposition of the beta-A4 peptide and to the pathogenesis of Alzheimer's disease. Expression and release of APP has also been known to mediate cell-matrix interactions and to participate in the regulation of cell proliferation." "Because of the specific processing of exportable proteins, thyrocytes represent a particularly useful cell type for the study of the processing of APP/APLP (especially proteolysis and iodination) as an indication of cell surface expression and for the study of the regulation of these functions." "The observations show the expression, maturation, and secretion of APP/APLP in **thyrocytes and the up-regulation of these processes by TSH.** Part of the immature APP/APLP appeared on the cell surface as indicated by its iodination. Apparently, this portion of immature APP/APLP escaped maturation during its transport to the cell surface."

Rinsho Shinkeigaku 1993 Sep;33(9):995-7. **[A case of Hashimoto's encephalopathy with a relapsing course related to menstrual cycle]** [Article in Japanese] Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Shoji S. "Hashimoto's thyroiditis was diagnosed on the basis of high thyroid microsomal titer and mild hypothyroidism. Neurological findings in admission included action tremor in both hands, myoclonus in all extremities, cerebellar ataxia, confusion, and hyperreflexia." "Hashimoto's encephalopathy was diagnosed from these findings. These episodes of remission and exacerbation were observed during the admission. **Her symptoms started at ovulation, worsened during the luteal phase, and improved when menstruation started. After the third relapse, she was treated with oral thyroxine for hypothyroidism and with an estrogen and progesterone combination to regulate the menstrual cycle.** Her thyroid function gradually became euthyroid and she did not experience any subsequent relapses. **The relation between the relapsing course and menstrual cycle suggests that the periodic alteration of gonadotrophic and/or gonadal hormones or the menstrual regulating center itself in the brain may be an important factor of pathogenetic mechanism of the disorder."**

J Clin Endocrinol Metab 1983 Jun;56(6):1164-8., **Thyroid-infiltrating T lymphocyte subsets in Hashimoto's thyroiditis.** Jansson R, Totterman TH, Sallstrom J, Dahlberg PA. "In Hashimoto's thyroiditis, the thyroid gland is infiltrated with immunocompetent lymphocytes." "We observed a relative decrease in intrathyroidal suppressor phenotype T (OKT 8+) cell numbers compared with peripheral blood (13% vs. 26%; P less than 0.01 by Wilcoxon signed rank test). This resulted in an increased helper to suppressor T (OKT 4+/OKT 8+) cell ratio (4.7 vs. 2.1; P less than 0.01). Within the gland, a significant local accumulation of B cells was also registered (27% vs. 12%; P less than 0.01). As to circulating lymphocyte subsets, no differences were found between 18 Hashimoto's thyroiditis patients and 26 normal subjects. Our results are compatible with a local synthesis of thyroid-directed antibodies and emphasize the importance of studying the local immunity in organ-specific autoimmune disease."

Endocr Rev 1996 Feb;17(1):45-63. **Thyroid hormone metabolism and thyroid diseases in chronic renal failure.** Kaptein EM. "Goiter and hypothyroidism may be induced by iodide excess, due to reduced renal iodide excretion, and may be reversed with iodide restriction in some patients."

Acta Med Austriaca 1999;26(4):126-8. **[Thyroid autoantibodies in depressive disorders]** [Article in German] Konig F, von Hippel C, Petersdorff T, Kaschka W. "We found autoantibodies (MAK, TAK, TRAK) in a high percentage (100 out of 144 = 70%) in severely depressed inpatients. Also we found a Hashimoto thyreoiditis in 5 patients." "We conclude that in cases of repeated depressive episodes especially depression of the elderly and in nonresponders it seems necessary not only to get lab for TSH, T3 and T4 but also to assess the autoimmune status of the thyroid gland (autoantibodies). There is further need for controlled studies whether there is a better outcome in nonresponders to antidepressive medical treatment and positive autoantibody status after supplementation with triiodothyronine."

Hokkaido Igaku Zasshi 1994 May;69(3):614-26. **[Screening for thyroid dysfunction in adults residing in Hokkaido Japan: in relation to urinary iodide concentration and thyroid autoantibodies]** [Article in Japanese] Konno N, Iizuka N, Kawasaki K, Taguchi H, Miura K, Taguchi S, Murakami S, Hagiwara K, Noda Y, Ukawa S. "The prevalence of thyroid dysfunction and its relation to thyroid autoantibodies (TAA) and urinary iodide concentration (UI) was studied in apparently healthy adults in Sapporo (n = 4110) (Sapporo group), and in five coastal areas of Hokkaido (n = 1061) (coastal group) which produce iodine-rich seaweed (kelp). The frequency of above normal UI (high UI) in the morning urinary samples of coastal group was 10.8%, significantly higher than that of Sapporo group (6.4%) ($p < 0.001$). Frequency of positive TAA in both groups were similar. In Sapporo group TAA was positive in 6.4% of males and 13.8% of females with an age-related increase." The overall prevalence of hyperthyroidism (TSH < 0.15 mU/L) in coastal group (0.6%) was similar to that in Sapporo group (1.1%), while that of **hypothyroidism (TSH > 5.0 mU/L) in coastal group (3.8%) was significantly higher than that in Sapporo group (1.3%) (P** < 0.001). The frequency of high UI correlated significantly with that of hypothyroidism with negative TAA ($r = 0.829$, $P < 0.05$), but not with positive TAA, or with that of hyperthyroidism. Hypothyroidism was more prevalent in TAA negative subjects with high UI than with normal UI. Moreover, serum TSH and thyroglobulin levels were higher and free T4 level was lower in former than in latter group. "These results indicate that 1) the prevalence of TAA negative hypothyroidism in iodine sufficient areas may be associated with the amount of iodine ingested, 2) **this hypothyroidism is more prevalent and marked in subjects consuming further excess amounts of iodine,** and 3) excessive intake of iodine should be considered an etiology of hypothyroidism in addition to chronic thyroiditis in these areas."

Endocrinology 1993 Jun;132(6):2645-53. **Thyroglobulin molecules internalized by thyrocytes are sorted in early endosomes and partially recycled back to the follicular lumen.** Kostrouch Z, Bernier-Valentin F, Munari-Silem Y, Rajas F, Rabilloud R, Rousset B. "Thyroglobulin (Tg) molecules stored in thyroid follicle lumens are heterogeneous in terms of iodine and hormone contents. It has been suggested that thyroid hormone is preferentially produced from the most highly iodinated Tg molecules and that thyrocytes are capable of selecting these molecules. The cellular localization as well as the molecular basis of such a selection process are not known." **"In** conclusion, our data show that 1) the thyroid apical endocytic process does not exhibit selectivity for Tg; 2) the thyrocyte possesses a sorting machinery for endocytosed ligands; and 3) internalized Tg molecules can be recycled back to the follicular lumen."

Autoimmunity 1997;26(3):173-87. **Effects of HgCl2 on the expression of autoimmune responses and disease in diabetes-prone (DP) BB rats.** Kosuda LL, Greiner DL, Bigazzi "We found that DP rats treated with mercury or water for a period of 40-125 days developed autoantibodies to thyroglobulin, with a higher incidence in HgCl2-injected animals (92% vs. 56% in

H2O-injected controls). A novel finding of our study was the detection of autoantibodies to laminin in the same rats, again with an increased incidence after HgCl2 treatment (83% vs. 44%)." "... while mercury does not seem to recruit, induce or rescue regulatory T cell function in DP rats, it does stimulate autoantibody responses in these animals."

Life Sci 1999;64(12):1037-44. **Thyroid stimulating hormone-receptor overexpression in brain of patients with Down syndrome and Alzheimer's disease.** Labudova O, Cairns N, Koeck T, Kitzmueller E, Rink H, Lubec G.

Cytopathology 2002 Feb:13(1):31-9. **Aspiration cytology of Hashimoto's thyroiditis in an endemic area.** Kumar N, Ray C, Jain S. "Hashimoto's thyroiditis (HT) is the second most common thyroid lesion next to endemic goitre diagnosed on FNA in iodine (I2) deficient areas." "In the present study the patients presented with HT a decade earlier than reported in I2 sufficient areas. Presentation as a nodular thyroid is common. Diagnosis of HT is likely to be missed in smears showing cytological evidence of hyperplasia or abundant colloid. HT was concurrent in 20 cases of endemic goitre."

JAMA 1994 Aug 3;272(5):364-70. **Thyroid diseases among atomic bomb survivors in Nagasaki.** Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M, Shimaoka K. "A significant dose-response relationship was observed for solid nodules, which include cancer, adenoma, adenomatous goiter, and nodules without histological diagnosis, and for antibody-positive spontaneous hypothyroidism (autoimmune hypothyroidism) but not for other diseases. The prevalence of solid nodules showed a monotonic dose-response relationship, yet that of autoimmune hypothyroidism displayed a concave dose-response relationship reaching a maximum (+/- SE) level of 0.7 +/- 0.2 Sv." "The present study confirmed the results of previous studies by showing a significant increase in solid nodules with dose to the thyroid and demonstrated for the first time a significant increase in autoimmune disease among atomic bomb survivors. A concave dose-response relationship indicates the necessity for further studies on the effects of relatively low doses of radiation on thyroid disease."

Int J Radiat Biol 2001 Apr;77(4):475-82. **Persistent subclinical inflammation among A-bomb survivors.** Neriishi K, Nakashima E, Delongchamp RR. "To investigate the associations between inflammation tests and radiation dose in A-bomb survivors." "The associations with radiation dose were statistically significant for leukocyte counts (71.0mm(-3) Gy(-1), p=0.015), erythrocyte sedimentation rate (1.58 mm h(-1) Gy(-1) , p = 0.0001), corrected erythrocyte sedimentation rate (1.14mm h(-1) Gy(-1), p=0.0001), alpha-1 globulin (0.0057 g dl(-1) Gy(-1), p=0.0001), alpha-2 globulin (0.0128 g dl(-1) Gy(-1), p=0.0001), and sialic acid (1.2711 mg dl(-1) Gy(-1), p=0.0001) but not for neutrophil counts (29.9 mm(-3) Gy(-1), p=0.17)." "Among inflammatory diseases, associations were the strongest for chronic thyroiditis and chronic liver diseases." "This study suggests statistically significant association between inflammation in A-bomb survivors and radiation dose of during 1988-1992."

Acta Endocrinol (Copenh) 1978 Aug;88(4):703-12. **A case of Hashimoto's thyroiditis with thyroid immunological abnormality manifested after habitual ingestion of seaweed.** Okamura K, Inoue K, Omae T. "An interesting case of iodide induced goitre with immunological abnormalities is described. The patient who was sensitive to synthetic penicillin had previously been treated for exudative pleuritis, congestive heart failure and acute renal failure. Following recovery, he began to ingest large amounts of seaweed after which he developed goitrous hypothyroidism. It was of interest that the serum level of gamma-globulin increased, and subsequently the antithyroid microsomal antibody became strongly positive, suggesting that thyroidal autoimmune processes had been precipitated. Biopsy of the thyroid gland revealed chronic thyroiditis, with evidence suggesting extreme stimulation by TSH." "While there is evidence suggesting that increased iodide may be an important factor in the initiation of Hashimoto's thyroiditis, this may result from the marked increased sensitivity of Hashimoto's gland to the effects of iodine."

Thyroid 2001 Mar;11(3):249-55. **One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit?** Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. "After 1 year of therapy with LT4, TPO-Abs and B lymphocytes decreased significantly only in the treated group of euthyroid patients with HT ($p < 0.05$). In contrast, TPO-Abs levels did not change or even increased in untreated euthyroid patients with HT." "Prophylactic treatment of euthyroid patients with HT reduced both serological and cellular markers of autoimmune thyroiditis. Therefore, prophylactic LT4 treatment might be useful to stop the progression or even manifestation of the disease."

Free Radic Biol Med 1999 Oct;27(7-8):901-10. **Thyroid status modulates glycoxidative and lipoxidative modification of tissue Proteins.** Pamplona R, Portero-Otin M, Ruiz C, Bellmunt MJ, Requena JR, Thorpe SR, Baynes JW, Romero M, Lopez-Torres M, Barja G. **"The levels of the glycation product N(epsilon)-fructoselysine (FL) and those of the oxidation products, N(epsilon)-(carboxymethyl)lysine (CML) and malondialdehyde-lysine (MDA-lys), identified by GC/MS in liver proteins, decreased significantly in hyperthyroid rats,** as well as (less acutely) in hypothyroid animals." "Cytosolic proteolytic activity against carboxymethylated foreign proteins measured in vitro was significantly increased in hypo- and hyperthyroidism."

Eur J Endocrinol 2002 Jun;146(6):777-81. **Vitamin D 1alpha-hydroxylase (CYP1alpha) polymorphism in Graves' disease, Hashimoto's thyroiditis and type 1 diabetes mellitus.** Pani MA, Regulla K, Segni M, Krause M, Hofmann S, Hufner M, Herwig J, Pasquino AM, Usadel KH, Badenhoop K. **"The vitamin D endocrine system plays a role in the regulation of (auto)immunity and cell proliferation."**

Clin Exp Immunol 1988 May;72(2):288-92. **The influence of the normal microbial flora on the susceptibility of rats to experimental autoimmune thyroiditis.** Penhale WJ, Young PR. "Female PVG/c strain rats maintained under **specific pathogen-free conditions until weaning were found to be significantly less susceptible to the induction of autoimmune thyroiditis by thymectomy and irradiation** than conventionally reared rats of the same strain." "It was found that the oral administration of antibiotics followed by fresh, homogenized, intestinal contents obtained from conventionally reared rats to newly weaned SPF PVG/c rats significantly augmented their autoimmune susceptibility." **"It is proposed that the composition of the normal gastrointestinal flora of conventionally reared rats profoundly influences susceptibility to the induction of autoimmune thyroiditis in this particular experimental model, possibly by antigenic cross-reactivity with thyroid tissue."**

Radiats Biol Radioecol 1996 Jul-Aug;36(4):632-40. **[The probable sequelae of thyroid damage from radioactive iodine during the Chernobyl accident]** Poverennyi AM, Shinkarkina AP, Vinogradova IuE, Beziaeva GP, Podgorodnichenko VK, Tsyb AF. "The analysis of the situation when children's thyroids were subjected to irradiation shows that tumors can most frequently develop as late as 20-30 years after irradiation. There are reasons to believe that tumors are induced by low dose of irradiation. The most important factor in development of pathologies is for sure the

age of the children of the moment of irradiation. A well-known consequence of the impact of radiation on the thyroid is the lymphocyte thyroiditis."

Clin Immunol Immunopathol 1996 Dec;81(3):287-92. **Iodine-induced autoimmune thyroiditis in NOD-H-2h4 mice.** Rasooly L, Burek CL, Rose NR. "Excess iodine ingestion has been implicated in induction and exacerbation of autoimmune thyroiditis in human populations and animal models." "Levels of serum thyroxin (T4) were similar in the treatment and control groups. Thyroglobulin-specific antibodies were present in the iodine-treated group after 8 weeks of treatment but antibodies to thyroid peroxidase were not apparent in the serum of any of the animals. Levels of thyroglobulin antibodies increased throughout the 8-week iodine ingestion period; however, no correlation was seen between the levels of total thyroglobulin antibodies and the degree of thyroid infiltration at the time of autopsy."

J Endocrinol Invest 2002 May;25(5):447-54. **Thyroid hormone autoantibodies in primary Sjogren syndrome and rheumatoid arthritis are more prevalent than in autoimmune thyroid disease, becoming progressively more frequent in these diseases.** Ruggeri RM, Galletti M, Mandolfino MG, Aragona P, Bartolone S, Giorgianni G, Alesci D, Trimarchi F, Benvenga S. **"To verify the greater prevalence of circulating thyroid hormone autoantibodies (THAb) in primary Sjogren syndrome (SS) vs Hashimoto's thyroiditis (HT) and Graves' disease (GD),** we measured THAb in the serum of patients with these 3 diseases who were sampled from 1998-1999 (no.=20, 88, 25) and 1990-1992 (no.=13, 75, 31)." "We found that IgG antibodies against T3, T4 or both were present with these prevalences in the 1975-1982, 1990-1992 and 1998-1999 series: HT=1, 4, 20%; GD=2, 6, 32%; SS=20, 31, 50%; RA=0, 12, 26%; other collagenoses=0, 0, 0%. The majority of the Sjogren or arthritis cases positive for THAb were negative for TGAb, while the opposite was true for the 2 autoimmune thyroid diseases. We conclude that prevalence of THAb in the 2 non-thyroid autoimmune diseases is greater than in the 2 thyroid autoimmune diseases. In addition, prevalence of THAb is increasing over time regardless of disease. **Molecular similarity between extra-thyroid connective proteins (specifically associated to primary SS and RA) and iodinated regions of TG,** and an increased preponderance of environmental factors as triggers of autoimmune diseases might account for our findings."

Endocrinol Metab Clin North Am 1987 Jun;16(2):327-42. **Environmental factors affecting autoimmune thyroid disease.** Safran M, Paul TL, Roti E, Braverman LE. "Exposure to excess iodine, certain drugs, infectious agents and pollutants, and stress have all been implicated."

J Immunol 1994 Mar 1;152(5):2586-95. **Ionizing radiation and autoimmunity. Induction of autoimmune disease in mice by high dose fractionated total lymphoid irradiation and its prevention by inoculating normal T cells.** Sakaguchi N, Miyai K, Sakaguchi S. "Ionizing radiation can functionally alter the immune system and break self-tolerance."

J Clin Endocrinol Metab 1995 Dec;80(12):3513-9. **Thyroid epithelial cells produce large amounts of the Alzheimer beta-amyloid precursor protein (APP) and generate potentially amyloidogenic APP fragments.** Schmitt TL, Steiner E, Klingler P, Lassmann H, Grubeck-Loebenstein B. "In view of the known association between familial AD and thyroid autoimmune disease, the expression pattern and cellular processing of APP in human thyroid cells were investigated." "The results of these studies demonstrated that APP isoforms 770 and 751 were expressed in fresh thyroid extracts as well as in cultured thyroid epithelial cells, with APP 770 being the predominant form. Compared to other types of cells, such as lymphocytes and fibroblasts, thyroid epithelial cells produced larger amounts of APP." "Interestingly, thyroid epithelial cells also contained larger C-terminal APP fragments of 21, 35, and 41 kDa. From the sizes of these fragments it could be deduced that they contained the entire amyloid beta sequence and were thus potentially amyloidogenic. The 41-kDa fragment was unique to thyroid cells. These fragments may be released into the circulation after thyroid cell damage. Increased/altered thyroid APP expression in familiar AD may induce alterations in thyroid epithelial cells and cell damage, and thus explain the frequent occurrence of thyroid autoimmunity in this disease."

Radiats Biol Radioecol 1994 Jan-Feb;34(1):3-7. **[Antibodies to the thyroid microsomal antigen in children and adolescents subjected to radiation exposure as a result of the accident at the Chernobyl Atomic Electric Power Station]** Shinkarkina AP, Podgorodnichenko VK, Poverennyi AM. "There is significant difference in the frequency of the antibody appearance between persons suffered from radioactive iodine and unsuffered ones. Correlation between levels of antimicrosomal antibodies and radiation dose obtained from incorporated radioactive iodine was not estimated."

Verh Dtsch Ges Pathol 1996;80:297-301. **[Spontaneous Hashimoto-like thyroiditis in cats]** Schumm-Draeger PM, Langer F, Caspar G, Rippegather K, Herrmann G, Fortmeyer HP, Usadel KH, Hubner K. "A breeding line of domestic cats spontaneously developing symptoms of hypothyroidism between the 40th and 60th day of life (fur changes, loss of appetite, growth retardation), elevated levels of antibodies against microsomal structures and thyroglobulin, and lymphocytic thyroid infiltration has been recently established at our facility. Aim of our studies was to examine the effect of high iodine ingestion or prophylactic thyroid hormone therapy on functional and morphological characteristics of this Hashimoto-like thyroiditis in cat. From birth to day 80 of life cats were treated with iodine (n = 9; 0.1 mg/l) or thyroxin (n = 13; 2.0 micrograms/ kg/d) respectively. Untreated animals served as controls (n = 12). Cat-serum was tested for thyroid function (TT3, TT4). After 8 weeks the thyroid tissue was submitted to routine histological processing (H&E) and the inflammatory activity was scored." "Both untreated hypothyroid (UHC) as well as iodine-treated (IC) cats revealed a significantly higher degree of thyroid inflammation and higher tissue levels of IgM as the thyroxin-substituted animals (TC)." **"Early thyroid hormone therapy significantly decreases both incidence and activity of autoimmune thyroiditis in cats as measured by inflammatory infiltration, IgM production and epithelial proliferation. Animals with excess iodide intake, however, show an aggravation of the autoimmune inflammatory activity."**

Vnitr Lek 1999 Sep;45(9):527-31. **[Reactions to metals in patients with chronic fatigue and autoimmune endocrinopathy]** Sterzl I, Hrda P, Prochazkova J, Bartova J, Matucha P. "Our study was designed to assess the effect of heavy metals on the severity of fatigue in autoimmune thyroid disease associated with autoantibodies against other endocrine organs." "Fatigue regardless of the underlying disease is primarily associated with hypersensitivity to inorganic and organic mercury, nickel, and gold. The groups differed in their hypersensitivity to other metals. In the control group, hypersensitivity--mostly to cadmium and lead--was found in four of the examined individuals only. Statistical analysis of data obtained from professionals and controls revealed a higher incidence of positivity to organic and inorganic mercury and nickel in professionals."

Neuroendocrinol Lett 1999;20(3-4):221-228. **Mercury and nickel allergy: risk factors in fatigue and autoimmunity.** Sterzl I, Prochazkova J, Hrda P, Bartova J, Matucha P, Stejskal VD. We

have found that fatigue, regardless of the underlying disease, is primarily associated with hypersensitivity to inorganic mercury and nickel. The lymphocyte stimulation by other metals was similar in fatigued and control groups. To evaluate clinical relevance of positive in vitro findings, the replacement of amalgam with metal-free restorations was performed in some of the patients. At a six-month follow-up, patients reported considerably alleviated fatigue and disappearance of many symptoms previously encountered; in parallel, lymphocyte responses to metals decreased as well. We suggest that metal-driven inflammation may affect the hypothalamic-pituitary-adrenal axis (HPA axis) and indirectly trigger psychosomatic multisymptoms characterizing chronic fatigue syndrome, fibromyalgia, and other diseases of unknown etiology.

The New England Journal of Medicine Volume 326:513-518 February 20, 1992 Number 8. **Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis.** N Takasu, T Yamada, M Takasu, I Komiya, Y Nagasawa, T Asawa, T Shinoda, T Aizawa, and Y Koizumi. "We determined the frequency with which thyrotropin-blocking antibodies were present in 172 hypothyroid patients with goitrous autoimmune thyroiditis (Hashimoto's disease) and 64 hypothyroid patients with atrophic autoimmune thyroiditis (idiopathic primary hypothyroidism). For 6 to 11 years we then followed 21 of these patients who were found to have thyrotropin-blocking antibodies. They received levothyroxine therapy for 3.5 to 8 years, after which it was discontinued." **"Thyrotropin-blocking antibodies were detected in 9 percent of the patients with goitrous autoimmune thyroiditis and in 25 percent of those with atrophic autoimmune thyroiditis. Among the 21 patients studied serially while receiving levothyroxine, thyrotropin-blocking antibodies disappeared in 15 (group 1), 7 of whom had goiter initially, and persisted in 6 (group 2), none of whom had goiter initially.** Levothyroxine therapy was subsequently discontinued in these 21 patients. Six of those in group 1 (four with goiter) remained euthyroid (mean follow-up after discontinuation of therapy, 2.1 years), and nine became hypothyroid again within 3 months. All six patients in group 2 remained hypothyroid. CONCLUSIONS. Hypothyroidism in some patients with autoimmune thyroiditis may be due to thyrotropin-blocking antibodies. The production of thyrotropin-blocking antibodies may subside, producing remissions of hypothyroidism. Chronic autoimmune thyroiditis may therefore cause transient as well as permanent hypothyroidism."

Clin Exp Immunol 1993 Mar;91(3):442-8. **Gender-related influences on the development of chronic graft-versus-host disease-induced experimental lupus nephritis.** Treurniet RA, Bergijk EC, Baelde JJ, De Heer E, Hoedemaeker PJ, Bruijn JA. "Autoimmune diseases are far more common in women than in men. **In the incidence of systemic lupus erythematosus (SLE), the female-to-male ratio is as high as 10:1. This suggests that sex hormones may play a fundamental role in determining the susceptibility to these diseases."** "After four cell transfers, female recipients developed a significantly higher albuminuria than both male groups. Serum concentrations of autoantibodies against glomerular basement membrane (GBM), collagen IV, and laminin were significantly higher in females 2-4 weeks after induction." "These findings indicate that: (i) in this model of lupus nephritis, susceptibility to glomerulonephritis is strongly influenced by sex-related genes; and (ii) among the variety of autoantibodies occurring in this model of SLE, both anti-GBM and anti-RTE autoantibodies play a key role in the pathogenesis of glomerulonephritis."

J Immunol 2002 Mar 1;168(5):2470-4. **A unique combination of inflammatory cytokines enhances apoptosis of thyroid follicular cells and transforms nondestructive to destructive thyroiditis in experimental autoimmune thyroiditis.** Wang SH, Bretz JD, Phelps E, Mezosi E, Arscott PL, Utsugi S, Baker JR Jr. "Compared with control animals, mice treated with IFN-gamma and TNF-alpha showed significantly sustained lymphocytic infiltration in the thyroid, which was associated with the destruction of portions of the follicular architecture at wk 6 after initial immunization." "Minimal apoptosis of thyroid epithelial cells was observed unless the mice were pretreated with IFN-gamma and TNF-alpha. These data demonstrate that this unique combination of inflammatory cytokines facilitates the apoptotic destruction of thyroid follicular cells in experimental autoimmune thyroiditis, in a manner similar to what is observed in Hashimoto's thyroiditis in humans."

Presse Med 2002 Oct 26;31(35):1670-5. **[Hypothyroidism related to excess iodine]** Wemeau JL. "Iodine-induced hypothyroidism is observed in fetuses, newborn, adults and in the elderly. It is observed in individuals without underlying overt thyroid disorder, and specially in patients with autoimmune thyroiditis or those previously treated for thyroid diseases (Graves' disease, subacute or pospartum thyroiditis, iatrogenic thyroid dysfunction...)." "The hormone deficiency is of obvious clinical expression, or sometimes discreet and revealed by hormone exploration. It is usually temporary, regressing with a few days or weeks after iodine withdrawal. Nevertheless, some patients require transient hormone replacement therapy."

Clin Exp Immunol 1982 Apr;48(1):196-200. **Thyroid antibodies are produced by thyroid-derived lymphocytes.** Weetman AP, McGregor AM, Lazarus JH, Hall R. "The significance of the characteristic lymphocytic infiltrate in the target organ in organ-specific autoimmune disease is unknown." **"The thyroid appears to be an important site of thyroglobulin antibody production but the thyroid lymphocytes also contain many** IgG PFCs of non-thyroglobulin specificity."

Nephrol Dial Transplant 1993;8(5):402-6. **Increased prevalence of thyroid peroxidase antibodies (TPO-Ab) in women with Glomerulonephritis.** Westman KW, Erfurth EM, Hagmar L, Bygren PG, Ericsson UB, Landin-Olsson M. "Women with glomerulonephritis had both a significantly greater prevalence of thyroid peroxidase antibodies (odds ratio 3.85, 95% confidence interval 1.04-14.3) and an increased prevalence of elevated serum TSH values (P = 0.007). No such difference was found in men."

Baillieres Clin Rheumatol 1996 May;10(2):259-71. **Hormones and autoimmunity: animal models of arthritis.** Wilder RL. "Hormones, particularly those involved in the hypothalamic-pituitary-gonadal and -adrenal axes (HPG and HPA), play important roles in various animal models of autoimmunity such as systemic lupus erythematosus in mice and collagen-induced arthritis (CIA) in mice and rats, and the streptococcal cell wall, adjuvant and avridine arthritis models in rats. Intimately linked to the subject of hormones and autoimmunity are gender, sex chromosomes and age." **"Oestrogens stimulate higher corticosteroid responses in females. The animal model data have major implications for understanding autoimmunity in humans.** In particular, adrenal and gonadal hormone deficiency is likely to facilitate T-cell dependent diseases like rheumatoid arthritis, while high oestrogen levels or effects, relative to testosterone, are likely to promote B-cell dependent immune-complex-mediated diseases such as lupus nephritis."

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Ray Peat's Newsletter

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Some issues related to the stress of winter:

"Winter sickness" occurs when there isn't enough daylight to allow us to recover from nocturnal stress. The stress related hormones rise at night, and winter nights are long.

The inadequate light produces thyroid and progesterone deficiencies.

A progesterone or thyroid deficiency, or estrogen and polyunsaturated fat excess, causes serotonin to increase. Cold, dark, and even minor stresses cause increased serotonin.

The amino acid tryptophan can be metabolized into serotonin, which can be converted into melatonin.

More than twenty years ago, tryptophan was being promoted as a sedative, even though it was known to be the only amino acid that is carcinogenic. In excess, it suppresses the function of the thyroid gland. A protein deficiency releases tryptophan from muscles.

A "serotonin deficiency" was often said to cause depression. Hydroxy tryptophan (5-HTP) is sold as a serotonin precursor that is supposed to improve mood. Many kinds of stress cause serotonin's activity to increase.

Melatonin has been sold as a sleeping pill, longevity pill, and anticancer agent. Its production in the body is stimulated by stress and darkness.

Light, especially red light, penetrates into the body, and suppresses free radical activity and activates the crucial respiratory enzyme, cytochrome oxidase, which is activated by thyroid, and which is inactivated by polyunsaturated fats.

Serotonin released from platelets causes blood clotting and vascular spasms, and stimulates cell division. It and histamine are mediators of inflammation that cause blood vessels to leak.

Serotonin triggers the release of the stress hormones, ACTH, cortisol, and prolactin.

People often gain weight during the winter; in the far north, blood tryptophan is elevated in the winter; depressed women have increased melatonin, alcohol lowers melatonin; alcohol consumption is increased by darkness.

The use of antiserotonin drugs in alleviating stroke, hypertension, heart failure, diabetes, depression, obesity, rheumatoid arthritis, lupus (SLE), fibrosis, wheezing, and migraine suggests the importance of hyperserotonemia in causing disease.

Postpartum, premenstrual, and seasonal serotonin soaks: Hints about aging, insomnia and diabetes

When I read, in the early 1950s, about the cyclical peaks of mortality in the early morning hours and winter months, that had been evident in actuarial tables for a long time, it wasn't hard to accept that light was good for us, and that darkness was harmful. "Chronobiology," the awareness that biological responses are dependent on the time of day, was firmly established by the 1950s.

"...Tryptophan transport was increased in the major depressions and in the dysthymic disorders." D. Pringuey, et al., 1986.

"...We propose that there is a hyperserotonergic state in the hippocampal formation of some subjects with schizophrenia...."
E. Scarr, D.L. Copolov, B. Dean, L. Rebecca.

"...a hyperserotonemic condition has been documented in preeclampsia."
Carrasco, et al., 2000.

"Both melatonin and serotonin were potent inhibitors of progesterone release."
Schaeffer and Sirotkin, 1997.

Beginning in the 1950s, when I would spend the summers working in the woods, I noticed effects of sunlight that I didn't understand, such as the worsening of acne in proportion to the amount of sun exposure, as well as during times of stress. In 1965, I noticed that even incandescent light exposure during the night could immediately provoke my acne, so I realized that ultraviolet irritation wasn't the essential factor. First I thought the eyes' consumption of vitamin A might be responsible, since taking additional vitamin A would control my acne, but then I realized that an

extended photoperiod stimulated the sex hormones, and that this increased demands for vitamin A.

When I moved to the northern US from Mexico in 1965, I began noticing other interesting hormonal and nutritional effects relating to the seasons. In the winter of 1966-67 I began referring to "winter sickness" as the consequence of the hormonal changes produced by a lack of light exposure. Women who moved from a sunny climate to cloudy Eugene, and who often lived in gloomy basement apartments while they were at the university, described premenstrual depression and other symptoms that they had never experienced before. Many serious diseases had their onset during these times of light deprivation and hormonal upset.

I submitted some of my observations on winter sickness to various journals, and didn't get any responses from most of the editors, except for occasional sarcastic remarks about how ridiculous it is to suggest that ***light*** would have biological or psychological effects on humans.

Since 1966 I had been including a discussion of light's effects in my classes on nutrition and hormones and aging, and in the early seventies I began travelling around to talk to health-food, alternative medicine, and church groups, and to talk on occasional radio and television programs, where I would emphasize the importance of good light along with good nutrition. I found that the general public, and especially so-called "conservative" people, were remarkably receptive to ideas of interactions between organism and environment, and between mood and chemistry. I think their receptiveness had to do with the attitude called "paranoia," an attitude that has its positive features, as Salvador Dalí observed.

Professional people, especially journal editors, on the other hand, seemed to suffer from a mental rigidity that was the polar opposite of paranoia, a belief that nothing was happening outside of the set of beliefs residing in their own minds. This is a psychiatric condition that can be called "editorness," or simply "professionalism."

Although no journal or magazine had responded favorably to my articles on winter sickness and light therapy, some of those editors later began publishing similar observations by themselves or others, and by 1985 "Seasonal Affective Disorder" was becoming something like a "movement," with people arguing about the proper use of "light panels" and phase-shifting of melatonin, and even direct supplementation of melatonin. When its factors are reduced to a minimum, usually two, a new thought can sometimes penetrate into the professional mentality, though they are likely to get one or both of those factors wrong, as often as not. The use of bright light to treat depression should have made people realize that a melatonin excess contributed to depression, but that simple idea has been generally evaded.

The reluctance to see any connection between mood and hormones, or between light and health, probably resulted from an education in which there was already an explanation for everything. Now that medicine accepts a role for light and hormones in mood and behavior, it is within a culture dominated by Estrogen Replacement Therapy and Selective Serotonin Reuptake Inhibitors, such as Prozac. When there is a product for everything, explanations are degraded, and professionalism reaches a new low. The use of Prozac and similar drugs to treat PMS is an example of how product-professionalism works. (Its action in PMS is probably the result of increasing a brain steroid, compensating for a progesterone deficiency, exactly contrary to the doctrine that it acts by increasing serotonin availability.)

People who believe that there is a "biological clock" in the brain think that light signals entering through the eye provide the cues that set the clock, and that the brain then organizes the behavior that's appropriate for the season and time of day. But pigeons wearing opaque hoods can sense environmental light if the rest of their body is uncovered. The same sort of bodily sensitivity to light was demonstrated by shining light onto the back of a person's knee.

Instead of a "clock" that consists of some procedure for counting enzyme reactions or DNA oscillations or something of the sort, for which there is not even a clear theory, I think the evidence supports the idea that physiological

states reflect the organism's relation to the environment, and that, in the absence of the necessary amount of light and heat from the environment, energy stores in the form of glycogen become depleted, creating hunger and a variety of stress reactions. It takes some time to deplete glycogen stores, and it takes time to assimilate food, and so hunger and satiation tend to be cyclic, but it isn't productive to call these processes "a biological clock."

Mitochondria change their shape and function during the night, becoming radically less effective at producing energy. Light regenerates the crucial cytochrome oxidase enzyme, creating the energy needed to repair mitochondria. During darkness, glycogen stores in the liver, brain and other tissues are used rapidly, because of the mitochondrial respiratory inefficiency. Fats are mobilized from storage under the influence of adrenalin that rises when glucose is scarce. Rapid eye movement sleep, the phase of active dreaming, increases with hunger, and the arousal subsides cyclically as adrenalin is suppressed by other adjustments, including increased cortisol, melatonin, GABA, and many other regulatory substances and processes.

Light suppresses melatonin and serotonin, but its action is biological and biochemical, not just informational--it's a component of our metabolism, not just a "cue." Our biological rhythms, of approximately 24 hours, do have a learned component, but Frank A. Brown's experiments in the 1960s made it clear that there are important rhythmic environmental influences other than the cycle of light and dark. Brown's biological experiments were complemented by Alexandre Rothen's physical experiments which made it clear that the diurnal cycles aren't just light cues. In the university's hamster house where I worked, the cycles of light and dark were automatically controlled, air temperature was kept constant, and there were no windows, but in the winter the hamsters' thymus glands practically disappeared, and then in the summer they were restored. The infrared and microwave radiation of the environment, that can penetrate walls, must be constant to avoid biological stress.

Winter, at least in some species, causes serotonin to increase. (Philo and Reiter, 1980) In the winter, and in the morning, intraocular pressure (IOP) increases (Qureshi, et al., 1999), and drugs that antagonize serotonin reduce IOP. Women, on average, have higher IOP than men, and estrogen increases IOP (and serotonin).

Serotonin is a mediator of inflammation that suppresses metabolism, disturbs blood pressure, and promotes clotting, so it would be a Manichean-seeming misfortune if it was also essential to have lots of it to experience eupohoria. But in reality a state of "serotonergia" is a state of torpor, discomfort, and depression, rather than a state of alert pleasure. Its levels are above normal in autism, attention deficit disorder, and some forms of mental retardation, as well as in various types of depression.

A mediator of stress transduces an infinite range of harmful influences into a stereotyped response, mobilizing the adaptive antistress systems. A relatively harmless stress, such as overheating, chilling, oxygen deficiency or exertion, can leave the organism stronger as a result of its adaptation, but other kinds of challenge, such as prolonged darkness, leave the organism more vulnerable despite its mobilization of its antistress systems. The difference seems to be that passivity allows a generalized catabolism, while an active response strengthens the functional system that is being challenged. Winter stress is a prolonged passive stress. The passive responses of hibernation, over-eating, lethargy or depression probably represent the best biological response under the circumstances, which have impaired the capacity for energetic response.

Depression, like inflammation, is a costly reaction for an organism that can't achieve a better adaptation. Serotonin is a mediator of both depression and inflammation. On the cellular level, serotonin depresses respiration, and on the organismic level it depresses body temperature which depresses biochemical reactions generally. For mood and mental function, it's probably significant that serotonin depresses blood circulation in the brain (Mendelow, et al., 1977; Eidelman, et al., 1978). There is no question about serotonin's being a mediator of depression, except

for the stereotype that got its start in the 1960s that wants to see it as a sedative euphoriant, a deficiency of which produces many psychological problems. The tryptophan and melatonin industries were built up around this serotonin myth.

Aging and the degenerative diseases involve combinations of metabolic depression and inflammation. Anti-serotonin agents are coming to be recognized as treatments for a wide variety of degenerative diseases.

Minks that have mated in the winter don't implant the fertilized ovum in the uterus until the spring equinox, when progesterone rises suddenly, and allows both the uterus and the embryo to begin the process of pregnancy and gestation. Progesterone provides the oxygen needed for the successful implantation of the embryo, while estrogen and serotonin lower the intrauterine oxygen.

Under good conditions, the (premenstrual) luteal phase of the monthly cycle resembles pregnancy, as a period of progesterone dominance, in which the abundance of progesterone causes cells to decrease their estrogen content. The luteal phase is actually the first stage of pregnancy, and if there is implantation of an embryo all of the processes that begin at ovulation progress continuously until childbirth occurs. When there is no implantation, the luteal phase progesterone dominance is terminated, allowing estrogen to enter tissues and producing menstruation. The sudden decrease of progesterone production before menstruation is similar to the decrease of hormone production just before childbirth. The same conditions that produce the premenstrual syndrome, if they aren't corrected by the placenta's massive production of progesterone, will produce preeclampsia, toxemia of pregnancy, eclampsia, and postpartum depression. They are also related to the problems that become so common at menopause. Whenever the production of progesterone falls, tissues are susceptible to estrogen.

There are several common causes of a progesterone deficiency. Deficiencies of thyroid, vitamin A, and cholesterol are often responsible for a progesterone deficiency. Inadequate light exposure can cause it. Excess polyunsaturated fats, interfering with gonads and thyroid, can cause it. And excess serotonin can cause it.

Serotonin is a precursor of melatonin, which tends to be produced at night. Because of the books published during the intensive marketing campaign for melatonin, many people are familiar with the work of Maestroni and Pierpaoli, who reported that treatment with melatonin, or with the transplantation of pineal glands from young animals, would extend the life span of mice and prevent cancer. Melatonin is often called the "pineal hormone," though there are other hormones in the pineal, and many other tissues can produce melatonin.

Mice and rats are nocturnal animals, so they are notoriously inappropriate for evaluating the nocturnal hormones as they might relate to humans and other animals that are active in the daytime. Although melatonin sometimes antagonizes serotonin in a protective way, in itself it can lower body temperature and alertness, ***suppressing thyroid and progesterone.*** (Sirotkin, 1997) Women who are depressed have been found to have higher daytime melatonin levels. (Danilenko, et al., 1994) While the popular books have given the impression that there is no question about the protective nature of melatonin, it turns out that **in only five out of 36 strains of inbred mice can melatonin be demonstrated in the pineal glands. The famous cancer prone strain, in which mammary cancer kills practically all the females, is one of these. When they are given melatonin the development of tumors is accelerated. When their pineal gland is removed, their life span is extended.**

Estrogen and stress increase free fatty acids, and unsaturated free fatty acids cause serotonin release; serotonin, at least under some circumstances, can be lipolytic, increasing the free circulating fatty acids.

Darkness creates stress, by free radical inactivation of the respiratory enzyme, cytochrome oxidase, and light restores the activity of that enzyme, and probably also has a variety of anti-free-radical actions. Free fatty acids rise in the darkness, intensifying free radical production and

suppressing respiration. Progesterone synthesis is suppressed by darkness. The serotonin liberated by the fatty acids suppresses progesterone by inhibiting the secretion of luteinizing hormone (LH) which stimulates progesterone synthesis, and also seems to act directly on the ovary to suppress progesterone secretion (Wilson, et al., 1975). While estrogen increases serotonin's actions, progesterone antagonizes them.

Serotonin depletes glycogen stores, much the way estrogen and histamine do. This can cause hyperglycemia. Thyroid, carbon dioxide, and caffeine, which inhibit serotonin release, all tend to protect glycogen stores. Under the influence of carbon dioxide, noradrenaline can still liberate glucose from glycogen, but serotonin's effect is inhibited by carbon dioxide.

Serotonin interferes with slow-wave sleep, creating a situation resembling that of depression or old age. Brain glycogen is depleted in old age, and this depletion contributes to inefficient brain metabolism. Serotonin's stimulation of ACTH, which stimulates the adrenal cortex, and its direct stimulation of cortisone production by the adrenals, is probably involved in the chronic excess of cortisone seen in depression and old age, which contributes to insulin resistance and diabetes, and to the atrophy of all tissues including the brain. (People who are studying chronic inflammatory processes are gathering data that will be meaningful for understanding depression and aging, but it seems that psychiatrists don't know about their work.)

Anti-serotonin drugs such as bromocriptine have been found to correct diabetes, apparently because serotonin interferes with the use of sugar, acting on cells' metabolism to decrease its use, and preventing the secretion of insulin. Bromocriptine's correction of obesity also seems to be the result of its correction of glucose metabolism.

In the 1970s, it was established that darkness increases the appetite for alcohol. More recently (Lin and Hubbard, 1995) it has been found that the antiserotonin drugs prevent the dark-induced appetite for alcohol. Alcohol is probably a self-medication to alleviate serotonin-related depression. Alcohol, like progesterone, is neuroprotective in brain trauma. Alcohol increases formation of the sedative neurosteroid ("THP") derived from progesterone (VanDoren, et al., 2000), and alcohol increases brain circulation, countering serotonin's effect.

Progesterone withdrawal and alcohol withdrawal are so closely related that one can alleviate the symptoms of the other.

Isolation might be another factor contributing to depression and alcoholism, since it decreases the formation of the protective neurosteroid.

The "brain fog" that is often described in depressed people (and people with other serotonin syndromes, such as the fibromyalgia syndrome) is probably produced by a combination of factors, including hypothyroidism, low body temperature, and hyperserotonemia. The amnesia produced by shock was found to be prevented by antiserotonin drugs (Montanaro, et al., 1979). The same researchers suggested that the drugs had an "antipunishment" effect, in effect making the animals less fearful.

There is more confusion in the medical literature regarding the actions of serotonin than there is about practically any other subject.

For example, there is clear evidence from both animal and human studies that serotonin, like estrogen, is associated with aggression, but the dominating stereotype is that serotonin is the agent of serenity and peace. In an epidemiological study (Moffitt, et al., 1998), a record of violence was clearly associated with above-average blood serotonin levels. Animal studies show that darkness stimulates both aggression and eating (Russell and Singer, 1983), and that serotonin increases, while antiserotonin drugs decrease, aggression (Carlini and Lindsey, 1983).

When lysergic acid derivatives came onto the pharmaceutical market, the spirit of the times caused them to be described as dopamine agonists, rather than as serotonin antagonists, but the latter would be at least as descriptive of their effects. Bromocriptine fulfills many of the requirements of being a serotonin antagonist, for example by suppressing prolactin. As a class, the serotonin antagonists have a very interesting place in pharmaceutical medicine, because the broad spectrum of their therapeutic activity suggests the

great variety of problems caused by excess serotonin.

The documentation of extensive government-supported fraud in research on LSD and marihuana should make us question subsequent research that plows the same or similar furrows. My inclination is to believe that incompetence can't account for the glaring errors in research on serotonin-related questions. Commercial commitments to particular theories of drug action have undoubtedly contributed to the crazy quality of the psychiatric serotonin literature.

In the case of some antiserotonin drugs, there is commercial support for research, so they might come into general use in spite of the mythic stature of tryptophan/serotonin/melatonin. But thyroid, protein, magnesium, thiamine, progesterone and light are natural factors that keep serotonin under control, and that don't have the side effects of the synthetic antiserotonergic agents. Knowledge of serotonin's harmful actions can guide our use of the natural protective factors. For example, whey protein contains much more tryptophan than whole milk or cheese does, and would tend to suppress the thyroid and activate the whole serotonin-stress system. Whey might be good food for fattening pigs, but its acceptance in the health food industry as a powdered protein supplement is just another example of the harmful effects of the serotonin mythology.

(Some comments on research methods:)

"Serotonin activity" may be judged by the response of prolactin to serotonin or to a drug that is thought to mimic serotonin, or by serotonin metabolites in cerebrospinal fluid, or by the total amount of serotonin in the blood, or by its efflux from platelets, or the ratio of its concentration in the plasma and in the platelets. It isn't very clear whether serotonin's concentration or its turnover rate is most important, and the number and sensitivity of the many "serotonin receptors" varies, and presumably changes the meaning of any given quantity of serotonin. When serotonin's activity is judged indirectly, interpretation and subjectivity are involved.

Even the "synaptic reuptake inhibitors," such as fluoxetine, sometimes relieve symptoms that are believed to be caused by an excess of serotonin (C. Advokat and V. Kutlesic, 1995, Neurosci Biobehav Rev 1995 Spring;19(1):59-66 Pharmacotherapy of the eating disorders: a commentary.)

But the actual injection of serotonin, or of serotonin antagonists that are known to approximately neutralize serotonin's effects, and the examination of the basal concentrations of the hormones known to be regulated by serotonin, are much less likely to be distorted by arbitrary interpretations.

When a "receptor" is first proposed or "discovered," it is always "a protein," though because of the idea of a barrier (semipermeable) membrane around cells, "membrane lipids" are sometimes invoked. But after a few years of research, the "receptor" becomes a more and more complex system of interacting molecules. The doctrine of the "receptor" is intended to explain why cells have a specific response to a specific substance. Gradually, a receptor becomes a "response element," but the "element," in its complexity, begins to shade off into the system "membrane/cytoplasm/nucleus," which is to say, the cell. ***The cell is the response element.*** *The "transmitter substance" interacts with various agonists, antagonists, inverse agonists and binding competitors to produce an effect that is a summation of influences. A single protein or protein system can serve as a "receptor" for antagonistic substances.*

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Int J Circumpolar Health 1998;57 Suppl 1:386-8. **Seasonal variation of the amino acid, L-tryptophan, in interior Alaska.** Levine ME, Duffy LK The seasonal pattern of L-tryptophan was studied in a Fairbanks, Alaska, population that was unadapted to the extreme light variations of the North. Previously, this population was shown to exhibit seasonal behavior effects such as increases in fatigue and sleep duration, as well as endocrine effects such as increases in melatonin levels and phase shifting. Caloric and macronutrient intake have been reported to vary seasonally in humans, thereby potentially

influencing the plasma levels of L-tryptophan, which is a precursor of serotonin and melatonin. Plasma levels of L-tryptophan from volunteers, whose average duration of stay in Alaska was eight months, were determined by automated amino acid analysis. Prominent results included finding increased levels in the winter **at several different diurnal time points. These findings support hypotheses which relate underlying physiological adaptations to the North to the increased incidence of behavioral disorders such as depression and alcoholism.**

Epidemiology 2000 Nov;11(6):660-5. **Alcohol consumption and urinary concentration of 6-sulfatoxymelatonin in healthy women.** Stevens RG, Davis S, Mirick DK, Kheifets L, Kaune W **"We found that the nocturnal urinary concentration of the primary metabolite of melatonin (6-sulfatoxymelatonin) decreased in a dose-dependent manner with increasing consumption of alcoholic beverages in the preceding 24-hour period, after taking into account the independent effects on melatonin of age, hours of darkness, use of medications that affect melatonin levels, and body mass index. A categorical analysis revealed no effect of one drink, but a 9% reduction with two drinks, a 15% reduction with three drinks, and a 17% reduction with four or more drinks."**

Fertil Steril 1993 Apr;59(4):896-900. **Baboon corpus luteum: the effect of melatonin on in vitro progesterone production.** Khan-Dawood FS, Dawood MY **"Melatonin (0.01 to 1.0 ng/mL) inhibited basal P production in all the CL (41.8 +/- 9.9 ng P without melatonin compared with 32.2 +/- 2.0 ng P, 28.4 +/- 2.1 ng with 0.01 and 1.0 ng/mL melatonin, respectively). Human chorionic gonadotropin-stimulated P production was significantly inhibited with as little as 0.01 ng of melatonin** (150.8 +/- 11.4 ng with 10 IU hCG versus 120.3 +/- 6.4 ng with 10 IU hCG and 1.0 ng melatonin). The degree of inhibition in the hCG-stimulated cells was greater than in the nonstimulated cells. Melatonin at a concentration of 0.001 ng/mL did not affect P production in both stimulated and nonstimulated cells. Serotonin in similar concentrations had no effect on luteal cell P production." "These findings indicate that melatonin exerts a suppressive effect on baboon dispersed luteal cell P production and thus may play a role in luteal function."

Experientia 1980 Jun 15;36(6):664-5. **A circannual rhythm in bovine pineal serotonin.** Philo R, Reiter RJ.

Exp Clin Endocrinol Diabetes, 1997, 105:2, 109-12. **Melatonin and serotonin regulate the release of insulin-like growth factor-I, oxytocin and progesterone by cultured human granulosa cells.** Schaeffer HJ; Sirotkin AV.

Physiol Behav 1983 Jan;30(1):23-7. **Relations between muricide, circadian rhythm and consummatory behavior.** Russell JW, Singer G Three forms of behavior--muricide, eating, and drinking--have been studied at six photic periods during a 12/12 hr light/dark circadian cycle to which the subjects have been habituated. One hundred and eight rats served as subjects, 18 per photic period. The frequency of muricide was recorded for each period and subsequent food and water intakes were measured during a 1 hr test period. **Results show a significantly higher frequency of muricide during the dark than during periods of light.** Food intake covaried significantly with the incidence of muricide rs = 0.89, p less than 0.05), while no such relationship was found between muricide and water intake (rs = 0.17, p less than 0.05). **The findings are consistent with reports of circadian changes in other rodent behaviors, including rhythmicity in home-cage and in shock-induced aggression.** Covariation of muricide and eating does not establish a causal relation between the two. Three models of physiological mechanisms which might provide substrates for the covariance are discussed.

Semin Clin Neuropsychiatry 2000 Apr;5(2):125-31. **Serotonin and amino acids: partners in delirium pathophysiology?** van der Mast RC, Fekkes D "Serotonin is one of the neurotransmitters that may play an important role in medical and surgical delirium. Normal serotonin synthesis and release in the human brain is, among others, dependent on the availability of its precursor tryptophan (Trp) from blood. **The essential amino acid Trp competes with the other large neutral amino acids (LNAA) tyrosine, phenylalanine, valine, leucine, and isoleucine for transport** across the blood-brain barrier. This competition determines its uptake into the brain, represented by the ratio of the plasma level of Trp to the sum of the other LNAA. The plasma ratio of Trp/LNAA, plasma level of Trp, and serotonin in plasma and platelets have been used as indirect peripheral measures for central serotonergic functioning. Both increased and decreased serotonergic activity have been associated with delirium. **Serotonin agonists can induce psychosis, both elevated Trp availability and increased cerebral serotonin have been associated with hepatic encephalopathy, and excess serotonergic brain activity has been related to the development of the serotonin syndrome of which delirium is a main symptom.** On the other hand, alcohol withdrawal delirium, delirium in levodopa-treated Parkinson patients, and postoperative delirium have been related to reduce cerebral Trp availability from plasma suggesting diminished serotonergic function. Rick factors for delirium such as severe illness, surgery, and trauma can induce immune activation and a physical stress response comprising increased activity of the limbic-hypothalamic-pituitary-adrenocortical axis, the occurrence of a low T3 syndrome, and, possibly, changes in

the permeability of the blood-brain barrier. There are indications that these changes have their effect on plasma amino acid concentrations, e.g., Trp, and multiple cerebral neurotransmitters, including serotonin. This stress response may be different depending on the stage of illness being acute or chronic."

J Neurosci 2000 Mar 1;20(5):1982-9. **Neuroactive steroid 3alpha-hydroxy-5alpha-pregnan-20-one modulates electrophysiological and behavioral actions of ethanol.** VanDoren MJ, Matthews DB, Janis GC, Grobin AC, Devaud LL, Morrow AL Neuroactive steroids are synthesized de novo in brain, yet their physiological significance remains elusive. We provide biochemical, electrophysiological, and behavioral evidence that several specific actions of alcohol (ethanol) are mediated by the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one (3alpha,5alpha-THP; allopregnanolone). **Systemic alcohol administration elevates 3alpha, 5alpha-THP levels in the cerebral cortex to pharmacologically relevant concentrations.** The elevation of 3alpha,5alpha-THP is dose- and time-dependent. Furthermore, there is a significant correlation between 3alpha,5alpha-THP levels in cerebral cortex and the hypnotic effect of ethanol. **Blockade of de novo biosynthesis of 5alpha-reduced steroids using the 5alpha-reductase inhibitor finasteride prevents several effects of ethanol.** Pretreatment with finasteride causes no changes in baseline bicuculline-induced seizure threshold but reverses the anticonvulsant effect of ethanol. Finasteride pretreatment also reverses ethanol inhibition of spontaneous neural activity in medial septal/diagonal band of Broca neurons while having no direct effect on spontaneous firing rates. Thus, elevation of 3alpha,5alpha-THP levels by acute ethanol administration represents a novel mechanism of ethanol action as well as an important modulatory role for neurosteroids in the CNS.

Clin Exp Pharmacol Physiol 2001 Jan; 28(1-2):70-3. **A proposed pathological model in the hippocampus of subjects with schizophrenia.** E. Scarr, D.L. Copolov, B. Dean, L. Rebecca.

Braz J Med Biol Res 1982 Oct;15(4-5):281-3. **Effect of serotonergic drugs on the aggressiveness induced by delta 9-tetrahydrocannabinol in rem-sleep-deprived rats.** Carlini EA, Lindsey CJ **1. delta 9-Tetrahydrocannabinol (THC) induced aggressive behavior in rats previously deprived of REM sleep. This aggressiveness was significantly potentiated by tryptophan and fluoxetine, drugs which increase brain serotonin** availability. 2. Conversely, **drugs which decrease serotonergic function such as D,L-p-chlorophenylalanine, cinanserin and cyproheptadine strongly blocked the aggressive behavior**. 3. On the basis of previous data indicating an involvement of dopaminergic mechanisms in this type of aggressiveness and the present results showing a role for serotonin, it is concluded that REM deprivation-THC aggression is under the control of at least these two neurotransmitters.

Endocrinol Exp 1979 Mar;13(1):9-18. **Inhibitory role of brain stem serotoninergic neuron system on thyroid function in rat.** Ruzsas C, Jozsa R, Mess B Thyroid function was investigated in adult male rats following the use experimental procedures which inhibit the activity of serotoninergic neuron system. Pharmacological blockade of the biosynthesis of sertonin by repeated administration of para-chlorophenylalanine (pCPA), or interruption (by Halasz knife) of the serotoninergic pathways of the brain stem which terminate on hypothalamic nuclei equally resulted in an augmentation of the following **parameters of hypothalamo-hypophysial-thyroid activity: T/S ratio, pituitary and blood TSH levels and blood thyroxine concentration as well as TRH content of the hypothalamus. The results suggest that the central nervous serotoninergic neuron system plays an inhibitory role in the regulation of TSH secretion, presumably** acting upon the hypothalamus, thereby inhibiting hypothalamic TRH secretion.

Vopr Onkol 2000;46(3):311-9. **[The effect of melatonin on the indices of biological age, on longevity and on the development of spontaneous tumors in mice].** Anisimov VN, Zavarzina NI, Zabezhinskii MA, Popovich IG, Anikin IV, Zimina OA, Solov'ev MV, Shtylik AV, Arutiunian AV, Oparina TI, Prokopenko VM, Khavinson VK Fifty female CBA mice were given melatonin with drinking water (20 mg/l) for 5 consecutive days monthly, beginning from the age of 6 months, until natural death. Another 50 intact mice were used as controls. Melatonin failed to significantly influence body weight or food consumption. **Age-related switching-off of estrus function was delayed, body temperature decreased. Somewhat decreased motor activity did not affect physical one or endurance. Increase in life span led to higher spontaneous tumor incidence.** Another experiment using 20 animals of the same line showed melatonin to inhibit free-radical processes. A conclusion was drawn that caution should be exercised before melatonin is recommended for long-term administration as a geroprotector.

Am J Psychiatry 1983 Jan;140(1):26-30. **Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders.** Stahl SM, Woo DJ, Mefford IN, Berger PA, Ciaranello RD **The authors found that platelet serotonin concentrations were significantly elevated in patients with chronic schizophrenia and in patients with bipolar major depressive disorder. High-affinity serotonin uptake was significantly reduced only in patients with bipolar major depressive disorder.** Thrombin-induced release of serotonin from platelets in any patient group was not

different from that of normal control subjects. Platelet serotonin storage in chronic schizophrenic patients was also not different from that in normal control subjects. These platelet findings could not be explained by age, sex, or medication variables. The authors suggest that the pharmacodynamics of platelet serotonin may be different in chronic schizophrenia than in bipolar major depressive disorder.

Arctic Med Res 1994 Jul;53(3):137-45 **Diurnal and seasonal variations of melatonin and serotonin in women with seasonal affective disorder.** Danilenko KV, Putilov AA, Russkikh GS, Duffy LK, Ebbesson SO In winters 1990-1991 and 1991-1992 women with and without seasonal affective disorder, winter type, were treated by light at 2500 lux either in the morning (0800h-1000h) or afternoon (1600h-1800h). In winter before light treatment, **melatonin levels in serum in daytime (1200h and 1600h) were higher in patients compared to controls ($p < 0.05$). This difference disappeared in the summer or** after light treatment in the winter. Also, light treatment and change in season resulted in a phase advance shift of melatonin rhythm in patients. The decline in melatonin levels correlated with the decline in specific SAD symptoms of hyperphagia and carbohydrate craving. In winter, neither patients nor controls showed significant diurnal variations in levels of whole blood serotonin. In both patients and controls, levels of serotonin were higher in summer as compared with winter, especially at 2000h. Our data suggest that elevated daytime melatonin can be a state marker of winter depression, and that seasonal change of photoperiod may also affect the circadian amplitude and daytime levels of blood serotonin.

Lik Sprava 1994 Jul-Aug;(7-8):88-90. **[The effect of an increased intensity of light on changes in the serotonin and melatonin content in patients with depression].** [Article in Russian] Bozhko GK, Tsaritsinskii VI, Kostiukovskaia LS, Kulabukhov VM Study into the effect of **light of increased intensity shows that in patients with anxious depression a high level of melatonin excretion declines to normal,** its low level in melancholic depression remaining unchanged. Blood **concentrations of serotonin in depressive patients are higher as compared with the healthy persons** and do not change with increasing in the brightness of the illumination **except for a decrease in a portion of patients showing maximum levels of serotonin and melanin.**

Brain Res Bull 1994;33(6):633-8. **The increased ethanol preference in rats induced by choice, darkness, or drugs is reduced by ritanserin.** Lin N, Hubbard JI We tested the hypothesis that ritanserin, a serotonin S2 antagonist, reduces voluntary and induced forms of ethanol drinking. We gave 10 mg/kg ritanserin IP or SC to groups of rats given either a) a free choice between 3% ethanol and water, or b) kept in the dark for 5 weeks and given a choice between a range of ethanol concentrations (3-25%) and water, or c) implanted with osmotic pumps filled with tetrahydro-beta carboline and given a choice between a range of ethanol concentrations and water. In each case, ritanserin significantly reduced ethanol consumption and ethanol preference for 8-10 days after the last injection.

Neuropsychobiology 1979;5(3):174-80. **Bromolysergide and methysergide protection against ECS-induced retrograde amnesia.** Montanaro N, Dall'Olio R, Gandolfi O Bromolysergide (BOL 148) and methysergide (UML 491), 2 mg/kg intraperitoneally, and saline were administered to rats 45 min before one-trial passive-avoidance conditioning followed by electroconvulsive shock (ECS) or sham-ECS (ECS). On test session (24 h later), the groups treated with both BOL 148 and UML 491 exhibited a clear-cut retention in comparison to saline-ECS rats. On the other hand, all drugged groups, regardless of their submission to ECS, showed a little less pronounced consolidation than saline-ECS rats. The antiamnestic effect **brought about by the two drugs was discussed in terms of receptor antagonism against ECS-released brain serotonin, whereas the lower passive-avoidance level** observed in treated animals was considered in relation to a possible **antipunishment effect of antiserotoninergic treatment.**

J Neural Transm 1981;50(1):1-12. **Depletion in amygdaloid 5-hydroxytryptamine concentration and changes in social and aggressive behaviour.** File SE, James TA, MacLeod NK 5,7-Dihydroxytryptamine (10 and 20 microgram) was microinjected bilaterally into **the amygdaloid complex of rats and resulted in 55% and 80% depletion in 5-hydroxytryptamine concentration, respectively. The lesioned animals exhibited fewer dominance behaviours and submitted more often to an intruder into their home-cages than did the vehicle-injected controls. The lesioned rats were also more submissive than were the controls when they were intruding into another** rat's territory. Only the higher dose of toxin altered social investigatory behaviour when this was measured in an arena in which neither rat had established territory. The lesioned rats displayed less social interaction and had reduced levels of motor activity. The results are compared with those of other studies in which there

has been regional or general depletion of brain 5-hydroxytryptamine concentration.

J Neuroimmunol 2000 Aug 1;108(1-2):131-5. **The pineal gland and cancer. I. Pinealectomy corrects congenital hormonal dysfunctions and prolongs life of cancer-prone C3H/He mice.** Bulian D, Pierpaoli W. **Hormonal derangements almost invariably anticipate and signal the onset of tumors.** Chronic, nocturnal melatonin administration delays aging in normal strains of mice. **On the contrary it promotes and accelerates the onset of tumors in the cancer-prone strain of C3H/He mice.** Grafting of a young pineal gland into aging mice prolongs their longevity and maintains juvenile circadian hormonal functions while pinealectomy (Px) does the opposite. We investigated if Px in C3H/He mice would modify their congenitally deranged pituitary function and affect their longevity. It was found that contrarily to Px in normal mice, Px in **C3H/He mice remarkably maintains juvenile night levels of thyroid hormones and lipids, preserves a cell-mediated immune response and significantly prolongs their life. The pineal gland and its pathology may be the key for understanding,** not only the causes of metabolic aging, but also the origin of those congenital or progressive aging-related hormonal alterations preceding onset of all tumors and thus allow preventive corrective interventions with pineal-derived agents.

J Pineal Res 1989;7(2):195-204. **Melatonin content of the pineal gland in different mouse strains.** Goto M, Oshima I, Tomita T, Ebihara S. Pineal melatonin content at several times during the day and night was measured in 36 inbred strains of mice (Mus musculus) kept under LD 12:12 cycles. The **results have indicated that only five inbred strains have pineal melatonin content, with higher levels during the night and lower levels during the day; the other 31 strains do not contain detectable melatonin in their pineal gland at any of times examined.** The former group includes two commonly used strains (C3H/He and CBA/Ms) and three wild-derived strains (Mol-A, Mol-Nis, MOM). C3H and CBA mice showed a similar pattern of pineal melatonin rhythm with a peak at 2 hours before lights on. The peak levels were about 150 pg/gland in both strains. The rhythmic patterns of melatonin content in Mol-A, Mol-Nis, and MOM were slightly different from those in CBA and C3H. In the wild-derived strains, the peak of melatonin content did not occur at 2 hours before lights on but tended to occur at midnight. The peak levels were 67-91 pg/gland at the highest point in these strains.

Am J Obstet Gynecol 1985 Sep 15;153(2):130-4. **The effect of serotonergic blockade in postpartum preeclamptic patients.** Montenegro R, Knuppel RA, Shah D, O'Brien WF Thirty postpartum preeclamptic patients from the University of South Florida Obstetrical Service were enrolled in a placebo-controlled, randomized, double-blind study to test the effectiveness of ketanserin in lowering the blood pressure. **An intravenous bolus of ketanserin resulted in a significant drop in the mean arterial blood pressure. The decrease in the blood pressure could be maintained by a continuous infusion of ketanserin.** Hypertension returned after the medication was discontinued. These observations suggest that ketanserin, a selective blocker of type II serotonin receptors, may be effective in **acutely reducing elevated postpartum blood pressure in preeclamptic patients,** and that serotonin may play a role in the pathogenesis of preeclampsia, but not be important as a mediator in the severity of the disease.

Eur J Pharmacol 1985 May 8;111(2):211-20. **Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5-HT receptor antagonists.** Ieni JR, Thurmond JB Drug treatments which influence brain serotonergic systems were administered to lactating female mice during the early postpartum period, and their effects on aggressive behavior, locomotor activity and brain monoamines were examined. P-chlorophenylalanine (200 and 400 mg/kg) and 5-hydroxytryptophan (100 mg/kg) inhibited fighting behavior of postpartum mice toward unfamiliar male intruder mice. These drug-treated postpartum females showed increased latencies to attack male intruders and also reduced frequencies of attack. In addition, postpartum **mice treated with the serotonin receptor antagonists, mianserin (2 and 4 mg/kg), methysergide (4 mg/kg) and methiothepin (0.25 and 0.5 mg/kg), displayed significantly less aggressive behavior than control mice, as measured by reduced** number of attacks. Whole brain monoamine and monoamine metabolite levels were measured after drug treatments. The behavioral results are discussed in terms of drug-induced changes in brain chemistry and indicate a possible role for serotonin in the mediation of maternal aggressive behavior of mice.

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Ray Peat's Newsletter

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Lungs, shock, inflammation, and aging

There is a growing effort by the food and drug industries, and many physicians, to promote the use of certain polyunsaturated fatty acids, those with their double bonds farthest from the acidic end of the molecule. These fats, which are found in fish, algae, and many vegetables, are the most easily oxidized of the common fatty acids. With stress, such as premature birth, and with aging, these fats produce free radical decomposition products at a high rate. They contribute to "shock lung" and to multiple organ failure.

After I had done my dissertation on the changes in oxygen metabolism that occur during aging and under the influence of estrogen, and not long after I had seen the therapeutic effects of progesterone in epilepsy, arthritis, depression, and multiple sclerosis, I met a woman who was disabled with some kind of inflammatory muscle and joint disease. Her face, arms, and upper torso were emaciated, but her hips and thighs were huge. This pattern of fat distribution is typical of the extreme and prolonged influence of estrogen.

In discussing her health history, she said that her movement problems began at the age of 21, when her physician-father began giving both her and her mother regular injections of estrogen.

Having a doctor in the family, they had the most complex medical studies done in trying to diagnose their problems. The thing that stood out in her description of the tests was the pulmonary oxygen diffusion test, which she said showed that both she and her mother had oxygen diffusing capacity that were "95% below normal." I think she might have meant that they were in the lowest 5 percent of the population, since I can't think of another interpretation that would be compatible with life. Right around that time, I read a study in which mice were given a large dose of estrogen, which, after just 40 minutes, caused a similarly radical decrease in their oxygen diffusing capacity.

In the late 1960s, I had been interested in the use by athletes of a drink made by foaming oxygen into a solution of gelatin, to increase their blood oxygenation and their performance. I tried to talk to a few physician-researchers about this, and they firmly said that it was nonsensical, because "blood is always fully oxygenated when it leaves the lungs." Looking in the science library at the university, I found a recent (c. 1968) study in which the blood's oxygenation was found to decline with aging, commonly down to about 50%. But despite the mouse study, I didn't find any studies regarding estrogen's effects on oxygen diffusion in humans. I believed that the reason was the same as the denial that athlete's blood might not be fully oxygenated, namely, a stupefying degree of authoritarianism and a need to absolutize anything that was in a medical textbook.

About 15 years later, I visited a friend who was 82 years old, who lived in Toluca, Mexico. When I first saw him, I could see that he didn't recognize me. He was sitting down, breathing heavily, and his face was purplish. He had been diagnosed as having emphysema, and hadn't been able to work for several weeks. Since he was very fat, I guessed that he might be suffering from the

". . . at a maximum level of exertion, the heart at high altitude is relying less on glycolysis (anaerobic energy production), and getting more of its energy from oxygen, than it would at sea level." This means that sea-level metabolism is more like cancer metabolism, because of the high oxygen/carbon dioxide ratio.

same sort of estrogen-provoked diffusion problem that I had run across previously. I left his daughter some progesterone and pregnenolone to give him, and left Toluca for several days. The next time I saw him, his skin had a better color, and his humor had returned. When I came back again two weeks after he had started taking progesterone and pregnenolone, his color was entirely normal, he had resumed working in his office (in a building that didn't have an elevator), and he insisted on taking me around the city, causing me to pant because of the altitude, about 8,500 feet above sea level.

In the 1950s, Gilbert Ling found that, under the influence of increased carbon dioxide, excitable cells don't "depolarize" electrically[1] to the extent that they do under a normal atmosphere. This principle has been applied to treat epilepsy, by breathing air with a few percent of carbon dioxide added, and more often, the principle has been used in the "diagnosis" of epilepsy, by using hyperventilation to induce seizures, by displacing too much carbon dioxide. Carbon dioxide spontaneously forms carbamino groups by reacting with the amino groups in proteins, and increasing the oxygen pressure causes the carbon dioxide to be displaced.

The binding of the acidic carbon dioxide to the protein molecule shifts electrons in the protein, making it more acidic. This shift in the protein changes the way the protein interacts with other molecules, including water, sodium, potassium, and calcium. Under the relatively acidic conditions when carbon dioxide is abundant, with the cell proteins' average electrons slightly "retracted," free radical production is inhibited, and cells are more resistant to radiation damage or other excitatory damage.

Carbon dioxide, along with the carbonic acid it forms as it reacts with water, regulates the organism's handling of water.

Carbon dioxide's association with cells has many effects, including the regulation of hormones and nerve transmitters. For example, carbon dioxide causes cells to bind serotonin, so that a loss of carbon dioxide causes serotonin to be released, with the effect that blood vessels become more permeable, and leak fluid (including serum proteins) into the surrounding spaces.

In the lungs, this leakage of fluid is very inconvenient.

In any tissue, the leakage of serum creates an additional barrier to the diffusion of oxygen from the blood to the tissue cells. The hypoxic cells release lactic acid and other mediators of inflammation, and the walls of the capillaries and other blood vessels thicken, making the proper circulation of the blood more difficult. These effects are usually overlooked in the brain and the heart, but in the lung they are hard to miss. Following a stressful death, the lungs are waterlogged, with a great increase in weight, a condition called "shock lung" or "wet lung."

The antiexcitatory action of carbon dioxide is opposed by oxygen, so oxygen can, in this context, be considered as a cell excitatory agent. At increased pressure, pure oxygen causes seizures, and even at normal pressure, the lungs are more likely to be damaged when there is more oxygen. Since the lungs' delicate membranes are in direct contact with air, it's obvious that they are in a vulnerable situation, easily losing too much carbon dioxide in the presence of excessive oxygen.

At high altitudes, once a person has adapted to the lower oxygen pressure, the tissues retain more carbon dioxide, and this prevents cells from being activated to the same extent that's possible at low altitude, so there is less lactic acid produced. The carbon dioxide makes the blood circulate more easily, so the heart works less to circulate the blood at the same rate that it would circulate at sea level, or even at a higher rate, and even **at a maximum level of exertion, it is relying less on glycolysis (anaerobic energy production), and getting more of its energy from oxygen, than it would at sea level.**

[1] In the normal resting state, a cell is "polarized." In the depolarized state, a cell is vulnerable, and if it is too frequently depolarized, it can be damaged or killed in the process called "excitotoxicity," and other related degenerative processes. Cancer cells are chronically "depolarized," and this is related to their low-efficiency metabolism.

Some people, who have a respiratory problem at sea level, react to high altitude by breathing so hard that they lose even more carbon dioxide than they were losing at low altitude, and they may develop lung edema, and even brain edema and seizures. With lung edema, breathing becomes harder, and the heart works harder. It has been discovered repeatedly over the years that altitude sickness can be treated successfully with supplemental carbon dioxide. The now-standard treatment for mountain sickness is the drug acetazolamide, which causes the body to retain carbon dioxide. Despite the drug's success in preventing and curing altitude sickness, there is a weird reluctance to acknowledge that mountain sickness is produced by an insufficiency of carbon dioxide. The same drug is now often used to treat sleep apnea, despite the textbooks' opinion that sleep apnea is caused by too much carbon dioxide, rather than by the alkalosis resulting from insufficient carbon dioxide.

If we think of the presence of lactic acid as evidence of metabolic inefficiency, then an athlete, or anyone who exercises strenuously, has a low degree of efficiency, especially at sea level. Despite the presence of oxygen that isn't being consumed at a maximum rate, glycolysis becomes very intense, producing lactic acid that apparently helps to limit the full use of the available oxygen. It is probably the high oxygen pressure, wasting carbon dioxide, that turns on the lower efficiency lactic acid-producing glycolysis.

"Hypoxemia of exercise," the failure of the blood to be fully oxygenated during strenuous activity, is very similar to the chronic hypoxemia that occurs in the "respiratory distress syndrome." Women ahtletes have a greater tendency to exercise hypoxemia then men. In the luteal phase, when progesterone should be dominant, women breathe more effectively than during the estrogen-dominated follicular phase of the cycle. Since estrogen, like exercise, causes blood vessels to leak fluid, this isn't surprising. Stress, such as exercise or sickness, causes a significant rise of estrogen, along with the other mediators of inflammation, even in men.

Both exercise and estrogen dominance cause fatty acids to be liberated from the tissues. The unsaturated fatty acids increase the permeability of capillaries, and the ratio of unsaturated fatty acids to saturated fatty acids corresponds closely to the degree of lung malfunction and respiratory distress. (Baughman, et al., 1984) The medium chain saturated triglycerides, extracted from coconut oil, can be used for intravenous feeding without causing the respiratory distress and lung damage produced by the unsaturated vegetable oils that were formerly used.

The long chain polyunsaturated fatty acids, including linoleic, linolenic, arachidonic, and docosahexaenoic (DHA) acids, cause mitochondrial breakdown, thyroid suppression, vascular permeability, brain edema, and increased radiation sensitivity.

DHA is the most unstable of these unsaturated fatty acids. But there is at present a very poweful marketing campaign which argues that DHA should be added to baby formula and should be taken by adults, because we supposedly "evolved on a diet rich in n-3 fatty acids," and because our tissues generally contain a much lower concentration of the n-3 fats than of the n-6 fats.

There is evidence that the low ratio of these n-3 fatty acids, such as DHA (docosohexaenoic acid), to the n-6 fats, such as arachidonic acid, is the result of the fact that the n-3 fats are extremely unstable, and break down rapidly in the tissues, producing lipid peroxides, free radicals, and the characteristic ethane, which can be measured in the breath. Stress accelerates the decomposition of these fats, and the resulting ethane can be detected in higher amounts during respiratory distress, and in premature babies and in older people.

Mead Johnson has announced that it will add DHA to their baby formula, arguing that it is an essential nutrient for eye and brain development. But animals that are fed a diet that is "deficient in" DHA are less susceptible to eye damage than animals that have "sufficient" DHA. But more generally, animals that are deficient in ***all of the so-called "essential fatty acids"*** are extremely resistant to all sorts of injury, shock, and poisoning.

Since all of the polyunsaturated fats inhibit thyroid function, and since the thyroid hormone is essential for the development of the brain and

lungs, increased use of polyunsaturated oils will increase the incidence of hypothyroidism, leading to the birth of more premature babies with lung disease. With a high concentration of polyunsaturated fats in the lungs, the exposure of the newborn's lungs to oxygen will create an inflammatory reaction. This is probably why the respiratory distress of prematurity usually takes a few days to appear. Considering what is known about oxygen, lungs, and DHA, I think it would be reasonable to say that increased use of DHA would be the ideal way to increase infant lung disease.

The unsaturated fats and estrogen contribute to the increased release of serotonin and nitric oxide (NO). Nitric oxide is produced during inflammation, and, like ethane, can be detected in the breath when the lungs are inflamed. Nitric oxide, as a pro-inflammatory free radical, stimulates the peroxidation of the unsaturated fats. Both NO and serotonin inhibit mitochondrial respiration, shifting metabolism toward glycolysis.

Since the processes that damage the lungs are so similar in aging, stress, and prematurity, I think an examination of the factors that cause premature birth will be useful for understanding the general problem of "lung stress."

Preeclampsia, or a syndrome of pregnancy induced hypertension, occurs in about 10% of pregnancies, and it's the main cause of maternal death and sickness of the newborn.

Thomas Brewer, about 50 years ago, made it clear that a protein deficiency is the main cause of preeclampsia. Protein deficiency causes a general inflammatory condition, with increased serotonin.

In women with preeclampsia, there are abnormally high levels of serotonin, nitric oxide, and lipid peroxidation.

In a study of more than 3000 women (Clausen, et al., 2001), the consumption of sugar and polyunsaturated fat was strongly associated with the development of preeclampsia. Women who don't eat enough protein are likely to substitute sugar and fat for the absent protein, so this study is consistent with Brewer's work, but it's very important to see that it was polyunsaturated fats, not saturated or monounsaturated fats, that caused the problem. Eclampsia (pregnancy- related seizures) and preeclampsia are caused by oxidative stress, produced by the excessive unstable fats. The increased serotonin and nitric oxide are exactly what would be expected to result from the high consumption of polyunsaturated fats, especially with a deficiency of protein in the diet.

Protein deficiency, like an excess of polyunsaturated fats, causes a thyroid deficiency. Supplements of thyroid, given during gestation, accelerate the maturation of the baby's lungs, and prevent the respiratory distress syndrome.

The use of adequate protein and saturated fats during pregnancy will prevent many of the problems of pregnancy and infancy, but since the unsaturated fats remain stored in the tissues for many years, and are mobilized during stress, it's important to eat correctly long before pregnancy. The requirement for vitamin E remains high for years after the diet has contained an excess of the polyunsatured fats.

The diet which protects the developing fetus happens to be the diet that protects adults from all sorts of stress, and prevents many of the worst symptoms of aging.

Supplemental thyroid, pregnenolone, and progesterone can partly make up for defects in the diet, by maintaining a better balance between carbon dioxide and lactic acid, and by restraining the various mediators of stress, such as NO, serotonin, and estrogen.

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plasma MDA and lipid peroxides increased ($P < 0.001$ and $P < 0.05$, respectively). Breath alkane output did not change significantly and vitamin E intake did not prevent the **increase in lipid peroxidation during menhaden oil supplementation. The results** demonstrate that supplementing the diet with n-3 fatty acids resulted in an increase in lipid peroxidation, as measured by plasma MDA release and lipid peroxide products, which was not suppressed by vitamin E supplementation.

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was a significant correlation (r = 0.89) **between the transfer factor at rest and the oxygen tension during maximal exercise in both the patients with restrictive and those with obstructive lung disease, but no correlation was found between the transfer factor and the resting oxygen tension. Exercise induced hypoxaemia (PO2 less than 8-8.5 kPa) occurred in some patients and this could be predicted with an excellent sensitivity and specificity if a discrimination point for the transfer** factor of 50 per cent of predicted or less was chosen. Determination of the transfer factor at rest is thus a good screening test for exertional hypoxaemia and can be used to select patients for exercise testing when the purpose is to detect hypoxaemia.

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Ray Peat's Newsletter

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Thought and energy, mood and metabolism

"Thought doesn't take any energy, thinking doesn't increase the brain's metabolic rate." For several decades, that was the received opinion of the professionals in psychology and neurology. An experiment was cited. But anyone who knew how to think knew otherwise: Hard thought would increase your temperature, prolonged hard thought would make you hungry, and if you didn't eat, prolonged hard thought could make you sick.

The energetic physiology of nerves and muscles had been studied and it was clear that a stimulated nerve expended energy and consumed energy at a higher rate than a resting nerve. The people who chose to believe the silly doctrine about brain metabolism had to believe that the activity of the nerves in the brain was no more intense during intense thought than at rest. It was something that should have been impossible to believe, sort of like the magic bullet theory of the Warren Commission, in which the bullet that killed the president later injured the governor in several places, leaving several metal fragments in his body, and then was found undamaged on a stretcher. With a strong reason to believe, anything can be believed, and the consequences of holding that belief can be great, seeming to validate the reason for choosing to believe.

Energy, thought, and language flow in one direction, through time, building up persistent structures. The structure of a flame, or of a sentence, is definite, but it takes its form from its situation. The symbolic aspect of language is trivial, subordinate to the energy that supports it.

God guard me from those thoughts men think
In the mind alone.
He that sings a lasting song
Thinks in a marrow-bone.
W. B. Yeats' "Prayer for old age":

In the nineteenth century, Sechenov had explained the brain's activity in terms of nervous reflexes. Vvedensky, Pavlov, and Anokhin had refined the implications of that view. But another school condemned the reflex theory of mental activity as crude materialism, and argued, like Descartes, that the brain's activity was immaterial, spiritual, and symbolic.

John Eccles, who was the most prestigious neurologist in England and America, argued that consciousness was completely immaterial. He took Heisenberg's "uncertainty principle" as a way to argue* that physical laws didn't really control the brain, that the whole system hinged on indeterminacy, and that the randomness of that hypothetical microscopic level provided a foothold for the immaterial soul in the brain. Noam Chomsky went directly from Descartes' view of the immaterial consciousness to human grammar, arguing that it was not necessary to investigate the brain at all, to be able to understand how we can produce and understand language. If a set of rules could "account for" or, in mathematical language, "generate," the grammatical structure of language, the rules would adequately describe the "genetic endowment" (itself a set of rules) that made language possible. The brain itself was to be treated as a "black box," whose function was to be inferred by

**Building any sort of superstructure upon the uncertainty principle is to get something from nothing. The uncertainty principle is a basis for nescience, not for knowledge.*

analysis of language (or, rather, by the devising of a set of rules which are consistent with the ways language is used), without examining the contents of the box.

Every field of cultural activity was affected by these doctrines that feared the identification of the mental and the material. Neokantianism introduced the idea that our perceptions are limited by our genetic endowment, and that as a result of that limitation, what we perceive is in reality only a symbolic abstraction.

In sociology, "symbolic interactionism," and in psychology, anthropology and linguistics various "structuralist" and "functionalist" doctrines offered antimaterialist ways to describe reality. Konrad Lorenz, serving as the theoretician of genocide, applied these ideas to anthropology and biology. Sociobiology and ethology are the current forms of Lorenz's doctrine. While symbolic interactionism has been used to justify cultural relativism, and sociobiology has been used to justify genocide, both of these seemingly opposite schools grew out of similar commitments to an abstracted and symbolic view of reality.

The school of "Artificial Intelligence" derives from, and is committed to, this immaterial, symbolic view of consciousness. The idea of "neural networks" would seem to have incorporated a material foundation, but actually it has only reassimilated the theoretical language that was used by the neurologists of the Eccles school of symbolic, immaterial, neurology. The image of a computer was imposed onto the brain, and then this theoretical description, in which "neural" no longer carried any substantial, metabolic meaning, was able to be used in its denatured form by the immaterialists.

In recent years, new technologies such as NMR/MRI have been able to show many metabolic details of the brain during different kinds of mental activity, and in different sicknesses. 25 years ago, N. P. Bekhtereva demonstrated that specific electrical patterns corresponding to a certain word or image could be identified in the brain, and recently the US CIA has funded research in which brain waves measured on the surface of the scalp can clearly show whether certain words or images have special significance for a person.

When the studies of brain chemistry and electrical activity are combined, it becomes clear that moods and meanings interact with metabolic processes in biologically rational ways, that have to do with adaptation of the organism to its environment. The "content" of our experience, and our substantial metabolism are so closely linked that there is no way to radically distinguish them.

R. D. Laing and Carl Rogers described the process of seeing the world as the client sees it, and they had valuable insights into the meanings of "psychopathology." But they still operated within a "symbolically constructed" reality, ignoring the metabolic, physiological aspects of their clients' problems.

The ability to perceive one's environment and adapt to it depends on having one's metabolic requirements met, and these chemical and physical issues are usually overlooked by psychiatrists, just as the issues of "meaning" may be overlooked by the physiologists.

Responding to particular people and particular demands can create organic and cellular patterns in which the glands, intestines, liver, nerves, and muscles adapt appropriately. The physiological pattern accomodates itself to the demands, but the organism's resources aren't always able to restore the original state, when the demands are no longer being made. Inadequate nutrition and inadequate stimulation limit adaptiveness, and create rigidity of behavior. Learned helplessness describes a global inability to adapt, that's produced by inescapable stress, but something like learned helplessness and unavoidable stress pervades our society, creating pathological rigidities.

The ability to perceive possibilities, and to act on those perceptions, requires biological resources, especially a high level of energy, but there must also be real possibilities in the environment. Several studies over the last forty years have shown that depressed and paranoid people have more accurate perceptions of their situation than happy optimists do.

The interlocking mental rigidities of millions of people are a problematic kind of adaptation. A

slight fluctuation in social relationships, such as losing a job or getting divorced, can cause tremendous changes in both perceived and real possibilities.

Dostoyevsky was interested in the "interlocking mental rigidities," and in various moral or spiritual alternatives. In Russian society, he said, psychopathology was the norm, lies could be therapeutic, and truth was the most poetic thing in the world ["Something about lying," 1873.] He used what might have been called, in the 20th century, themes of ***"anomie,"*** to explore consciousness and values. "Everything is meaningless," or "everything is lawful," instead of leading to suicide or crime, could lead to an exalted view of life's possibilities. Dostoyevski wrote about his own "nervous illness," that included alternating depression and ecstasy, and that has been considered to be some sort of epilepsy or schizophrenia. Whatever his mental illness was, he had a remarkable recovery when he was arrested and sent to prison. Before his arrest, he had been on a vegetarian diet, but in the prison in Siberia he was given a daily portion of hamburger.

Many people have experienced a dramatic improvement of mood when they began eating more protein. On a low protein or starvation diet, the body experiences, in different proportions, the "stress" reaction and the "hibernation" reaction.

An immediate reaction to hunger is to secrete adrenalin, which draws glucose from the liver and fats from the fatty tissues. When the liver's glycogen is depleted, cortisol is produced to mobilize amino acids from muscles and other tissues, to provide energy.

Muscle protein is very rich in tryptophan and cysteine, and these amino acids suppress the thyroid gland's function, and are potentially toxic to nerves, especially in the presence of cortisol and hypoglycemia. Tryptophan is turned into serotonin, which promotes lipid peroxidation, blood clotting, and certain patterns of nerve activity. Serotonin can suppress mitochondrial respiration, and along with the reduced body temperature that it produces, a pattern of torpor or helplessness tends to be produced.

But another pattern can be produced by stress, in which adrenaline and related substances maintain body temperature and alertness, despite the metabolic inefficiency. In hypothyroidism, it is common for adrenaline or noradrenaline to be produced in very large amounts. The brain and pituitary hormones (thyroid stimulating hormone, TSH, and its release hormone, TRH) that tend to increase in hypothyroidism, have their own brain modifying effects, increasing alertness and attention. Hypothyroidism can also cause hypersecretion of ACTH, adrenocorticotropin, which is also a powerful brain stimulant.

These two different reactions to stress, viz., torpor or tension, depression or hyper-alertness, are often seen as reactions to over-sleeping, or under-sleeping. On a Sunday, when a person sleeps an extra hour or two, it's common to feel lethargic for the rest of the day. And when a person has to get up several hours too early, there is often the feeling of being over-stimulated.

Many years ago, someone noticed that depressed people who missed a night's sleep, or who were wakened several hours earlier than normal, came out of their depression, until they caught up on their sleep. Sleep deprivation has become a recognized treatment for depression.

Manic-depressive ("bipolar") people typically seem to need very little sleep during their manic periods.

In depression, there is excessive influence of serotonin, in mania, excessive influence of adrenaline. These chemicals are links between energy metabolism and many specific adaptive physiological processes. One pattern of nerve activity, corresponding to these metabolic patterns, inclines a person to see the impossibility or futility of everything, the other causes an inclination to overlook impediments and undesirable consequences. In either state, important parts of reality are excluded.

Apart from these moods that can be induced by the interactions of diet, hormones, and the demands or opportunities of the envirnoment, the liveliness and vigor of metabolism influence the rhythms of thought and behavior, and the richness of experience and the appropriateness of activities. On a superficial level, our ability to

handle information can be compared to that of a computer, but that metaphor neglects our natural existence, that is like a vortex of biochemical and physical interactions, as well as being an assimilator and projector of impressions, meanings, and intentions. In a computer, the information being processed is separate from the hardware doing the processing, but in us, there is no information, message, content, or memory that is distinct from our living substance. Living substance isn't a collection of distinct objects that can be in this state or that state, because living substance is a process, always renewing itself with more or less appropriateness for its changing situations. Every state of consciousness is a state of being.

Let's look briefly at the way Anglo-American neurology came to look at the brain as a computer. For many years, the dogma said that the brain-computer was "hard wired," meaning that the arrangement of the nerves was genetically determined, set forever during fetal life, and altered only as individual nerve cells died during learning and aging. Since computer wires carried only on/off signals, nerves would carry only on/off signals: When a nerve "fired," it was said to be analogous to an "on-current," and the rest of the time it was "off." The nerve's electrical activity (contrary to clear evidence) was dogmatically identified with the superficial "lipid bilayer membrane," which was said to have only two states, open and closed. This abstract and incorrect description of an individual nerve was originally adopted because many neurologists, in the days before computers, wanted to be able to describe the brain as "a telephone swithchboard," handling messages, however, that were as simple as the patterned clicks of telegraphy. Information was one thing, the switching machinery was another thing.

The school of Pavlov (contrary to Anglo-American dogma) set out to understand consciousness, so when they thought of nerves, they avoided assumptions derived from telegraphy. There has never been any good reason to view nerves as wires carrying only simple "telegraphic" information. P. K. Anokhin, in his last book, discussed the reasons for believing that individual nerves handle complex information complexly. In practical fields, such as the physiology of hearing, there has been recognition that individual nerves seem to transmit qualitative, complex, messages.

The idea of a "hard-wired" computer-like brain was conditioned at every level by the philosophy of the immateriality of consciousness. The idea of telegraphic electrical impulses hardly changed when "neurotransmitter" chemicals were discovered: They just provided links between the filaments that still carried only on/off information. The idea that nerve cell metabolism ***is*** consciousness is still excuded from the ruling doctrine.

Since I have been interested in the way that hypothyroidism, a T3 deficiency, causes sleep problems, I have seen similar patterns in several seemingly different conditions. At menopause, insomnia, hypothyroidism, and diabetes are likely to develop along with hot flushes. Although hypothyroidism often causes the temperature to be subnormal, I saw many women whose temperature before breakfast was normal, but then fell after breakfast, usually following some hot flushes and sweats. Gradually, I began to realize that this corresponded to extremely high adrenalin and cortisol in the morning, and that high morning temperature was sometimes the first sign of the developing "hyper-alert" state, though most often it just represented the stress and exhaustion that result from disturbed, inefficient, sleep.

Using a small dose of T3 normally causes an increase of temperature and pulse rate, but in these people who are in an extremely adrenergic state, the T3 causes both the temperature and heart rate to decrease, as it restores metabolic efficiency. Then, as the stress state disappears, the thyroid supplements will gradually begin to bring the metabolic rate, temperature, and pulse up to normal. When a normal body temperature is maintained by thyroid-supported respiration, rather than by the stress hormones, sleep is efficient.

Thyroid, especially T3, has been commonly used in the treatment of depression, and there are many indications that, as it relieves the depression, it is also correcting a state of stress, lowering the cortisol which is typically

chronically increased in depression, and making sleep restful, rather than debilitating.

Women are especially susceptible to depression, diabetes, hypothyroidism, osteoporosis, Alzheimer's disease, and many other conditions that derive fairly directly from impaired energy metabolism. Some people have proposed that psychiatric problems are equivalent to "neural diabetes." "Syndrome X" (insulin resistance with heart symptoms) represents an advance toward seeing energy metabolism as the central biomedical issue.

Adequate dietary protein, and the ability to use it efficiently, should have the highest priority in the treatment and prevention of nervous and emotional problems, regardless of whether the diagnosis is "bipolar disorder," "depression," "schizophrenia," "multiple sclerosis," "obsessive compulsive disorder," or other official psychiatric category.

Without other nutrients, including sugar, much of the dietary protein is converted to energy, and without good thyroid function, protein can't be used properly. Whey, soy protein, and other industrial by-products sold as protein supplements aren't safe. Eating a variety of animal proteins, with some fruits and potatoes, is the safest way to prevent the metabolic disruptions caused by protein malnutrition.

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Endocrinology 2000 Mar;141(3):1027-40. **Effects of pharmacological and nonpharmacological treatments on thyroid hormone metabolism and concentrations in rat brain.** Eravci M, Pinna G, Meinhold H, Baumgartner A. "The activities of the 5'I-deiodinase (5'D-I), 5'II deiodinase (5'D-II) and 5III-deiodinase (5D-III) isoenzymes and tissue concentrations of thyroxine (T4) and triiodothyronine (T3) were measured in up to 10 regions of the rat brain **after acute and subchronic nonpharmacological (sleep deprivation, 12 h fasting, 14 days' calorie-reduced diet)** and pharmacological (ethanol, haloperidol, clozapine, lithium, carbamazepine, desipramine, fluoxetine, tranylcypromine, and mianserin) treatments. All of these treatments induced significant and sometimes dramatic changes in 5'D-II activities and tissue concentrations of thyroid hormones and, to a lesser extent, in 5D-III activity. The activity of 5'D-I remained unaffected. The results revealed a surprising specificity for each type of treatment in terms of the isoenzyme and hormone affected, the direction of the change, the brain region affected and the time of day. The changes in thyroid hormone concentrations frequently failed to correspond in any way to those in deiodinase activities and unexpected effects such as inhibition of both 5'D-II and 5D-III were seen, indicating that there may be additional pathways of iodothyronine metabolism in the CNS. In conclusion, particularly 5'D-II activity and thyroid hormone concentrations in the CNS are highly sensitive to many different kinds of influence that may induce changes in neuronal activity. However, these changes in deiodinase activities do not ensure stable tissue concentrations of T3, but were, on the contrary, in most cases accompanied by marked changes T3 levels in the tissue."

Nihon Shinkei Seishin Yakurigaku Zasshi 1999 Oct;19(4):139-46 **[The influence of L-triiodothyronine on the action of desipramine on beta and serotonin 2A receptor, monoamines in the rat brain].** [Article in Japanese] Watanabe A Department of Neuropsychiatry, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Japan. The co-administration of thyroid hormone and antidepressants is often useful in the treatment of refractory depression. **The aim of this study is to clarify the anti-depressive mechanisms of repeated co- administration of thyroid hormone (T3) and desipramine (DMI) in the rat brain.** Forced swimming test, open-field test, monoamine contents, beta receptor, and serotonin (5HT)2A receptor were compared in four experimental groups (control, T3, DMI, DMI+T3). In the forced

swimming test, the (DMI+T3) group showed a significantly decreased immobility time compared with that of the control group. **The noradrenaline (NA) content in the prefrontal cortex was highest in the (DMI+T3) group. Although beta receptor was not altered in any brain region in the (DMI+T3) group, 5HT2A receptor was significantly decreased,** and the dopamine (DA) turnover rate was significantly increased in the prefrontal cortex. This study suggests that the addition of T3 enhanced the action of DMI alone on the monoaminergic system in the prefrontal cortex.

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Ray Peat's Newsletter

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Intelligence and metabolism

Appropriate stimulation is an essential part of the developmental process. Inappropriate stimulation is a stress that deforms the process of growth. Mediators of stress, such as serotonin, can cause persistent distortions of physiology and behavior.

Education can either activate or suppress mental energy. If it is mainly obedience training, it suppresses energy. If it creates social dislocations, it disturbs mental and emotional energy.

Stress early in life can impair learning, cause aggressive or compulsive behavior, learned helplessness, shyness, alcoholism, and other problems.

Serotonin activates the glucocorticoid system, which can produce brain atrophy. Antiserotonin agents protect against brain atrophy and many other effects of stress. The brain-protecting neurosteroids, including pregnenolone and progesterone, which are increased by some kinds of stimulation, are decreased by isolation stress, and in their absence, serotonin and the glucocorticoids are relatively unopposed.

Since excess serotonin can cause thrombosis and vasospasms, and the excess cortisol resulting from hyperserotonemia can weaken blood vessels and the immune system, a person's longevity is likely to be shortened if something doesn't intervene to alter the patterns induced by stress early in life.

Having written about animal intelligence, and the ways in which it is similar to human intelligence, now I want those ideas to serve as a context for thinking about human intelligence without many of the usual preconceptions.

Intelligence is an interface between physiology and the environment, so it's necessary to think about each aspect in relation to the other. Things, both biochemical and social, that enhance intelligence enhance life itself, and vice versa.

Psychologists have tried to give their own definitions to words like idiot, imbecile, moron, and genius, but they have just been refining the clichés of the culture, in which "dummy" is one of the first words that kids in the U.S. learn. Many psychologists have tried to create "culture-free" tests of intelligence, making it clear that they believe in something like innate animal intelligence, though they usually call it "genetic" intelligence. Other psychometrists have transcended not only biology but even rationality, and have catalogued the ***preferences*** of people that they define as intelligent, and designed "I.Q. tests" based on the selection of things that were preferred by "intelligent people." This behavior is remarkably similar to the "psychometry" of the general culture, in which "smart" people are those who do things the "right" way.

Baroness Blatch: "My Lords, the levels of achievement are well above the national average of our own state schools."

"This is a school which attained 75 per cent A to C passes in 1998, and 63.9 per cent in 1999. Those figures are well above national averages. There is no truancy; and there is the highest possible level of parental satisfaction with the school. When those parents are paying their money and know what they are paying for, who are we to take a different view about the philosophy of education in a private school?"

Comment during debate in House of Lords, June 30, 1999, on Chief Inspector of Schools Woodhead's threat to close Summerhill, a democratic school which had been started in 1921.

In 1927, the government inspectors had recommended that 'all educationalists' should come to Summerhill to see its 'invaluable' research, which demonstrated that students' development is better when they regulate themselves and are not required to attend lessons.

About thirty years ago, someone found that the speed with which the iris contracts in response to a flash of light corresponds very closely to the I.Q. measured by a psychologist using a standard

intelligence test. The devices used to measure reaction time in drivers' education courses also give a good indication of a person's intelligence, but so does measuring their heart rate, or taking their temperature. Colleges would probably be embarrassed to admit students on the basis of their temperature (though they commonly award scholarships on the basis of the ability to throw a ball). Colleges, to the extent that they are serious about the business of education, are interested in the student's ability to master the culture.

The way a person has learned during childhood can shape that person's manner of grasping the culture. To simply accelerate the learning of a standard curriculum will increase that person's "I.Q." on a conventional test, but the important issue is whether it is really intelligent to learn and to value the things taught in those curricula. Some educators say that their purpose is to socialize and indoctrinate the students into their discipline, others believe their purpose is to help their students to develop their minds. Both of these approaches may operate within the idea that "the culture" is something like a museum, and that students should become curators of the collection, or of some part of it. If we see the culture metaphorically as a mixture of madhouse, prison, factory, and theater, the idea of "developing the student's mind" will suggest very different methods and different attitudes toward "the curriculum"

Even sophisticated people can fall into stereotyped thinking when they write about issues of intelligence. For example, no one considers it a sign of genius when a slum kid is fluent in both Spanish and English, but when some of history's brightest people are discussed, the fact that they learned classical Greek at an early age is always mentioned. No one mentions whether they were competent in idiomatic Spanish.

One of the old cultural stereotypes is that child prodigies always "burn out," as if they were consuming a fixed amount of mental energy at an accelerated rate. (This idea of burn-out is isomorphic with the other cultural stereotypes relating aging to the "rate of living," for example that people with slow heart beats will live longer.) Some of the men who have been considered as the world's brightest have, in fact, gone through a crisis of depression, and Terman's long-term study of bright people found that "maladjustment" did increase with I.Q., especially among women. But the facts don't support the concept of "burn-out" at all. I think the facts reveal instead a deep flaw in our ideas of education and professional knowledge.

In a world run by corporation executives, university presidents ("football is central to the university's mission"), congressmen, bankers, oilmen, and agency bureaucrats, people with the intelligence of an ant (a warm ant) might seem outlandishly intelligent. This is because the benighted self-interest of the self-appointed ruling class recognizes that objective reality is always a threat to their interests. If people, for example, realized that estrogen therapy and serotonin-active drugs and x-rays and nuclear power and atomic bomb tests were beneficial only to those whose wealth and power derive from them, the whole system would lose stability. Feigned stupidity becomes real stupidity.

But apart from ideologically institutionalized stupidity, there are real variations in the ability to learn, to remember and to apply knowledge, and to solve problems. These variations are generally metabolic differences, and so will change according to circumstances that affect metabolism. Everyday social experiences affect metabolism, stimulating and supporting some kinds of brain activity, suppressing and punishing others. All of the activities in the child's environment are educational, in one way or another.

Some of the famous prodigies of history illustrate the importance of ideology in the development of intellect. Family ideology, passing on the philosophical orientations of parents and their friends, shapes the way the children are educated.

Some of these family traditions can be traced by considering who the child's godfather was. Jeremy Bentham was John Stuart Mill's godfather, Mill was Bertrand Russell's; Ralph Waldo Emerson was William James' godfather, James was W. J. Sidis's. Willy Sidis was educated by his parents to demonstrate their theory of education, which grew out of the philosophies of Emerson and James. His father, Boris Sidis, was a

pioneer in the study of hypnosis, and he believed that suggestion could mobilize the mind's "reserve energy." Willy learned several languages and advanced mathematics at an early age. After he graduated from Harvard at the age of 16, he tried teaching math at Rice Institute, but he was displeased by the attitudes of his students and of the newspaper and magazine writers who made a profession of mocking him. He attended law school at Harvard, and would have been imprisoned as a conscientious objector if the war hadn't ended.

Antisemitism probably played a role in his sense of isolation when he was at Harvard and Rice. In 1912 Henry Goddard, a pioneer in intelligence testing (and author of ***The Kallikak Family: A Study in the Heredity of Feeble- Mindedness***), administered intelligence tests to immigrants and determined that 83 percent of Jews and 87 percent of Russians were "feeble-minded." By the standards of the time, it was highly inappropriate for the child of extremely poor Jewish immigrants from eastern Europe to be so bright.

Sidis hid from the press, and worked as a bookkeeper and clerk, while he studied and wrote. During his years of obscurity, he wrote books on philosophy and American history. Eventually, the journalists discovered him again, and after prolonged lawsuits against the magazines for invasion of privacy and slander, he died of a stroke at the age of 46.

Sidis is probably the culture's favorite example of the child prodigy who burns out, but people (Robert Persig, Buckminster Fuller) who have read his books have said favorable things about them. The journalists' emphasis on the fact that Sidis never held a prestigious job nicely illustrates their cliché mentality: "If you're so smart, why aren't you rich?" But throughout history, intelligent nonconformists have supported themselves as craft-workers or technicians--Socrates as a stone mason, Spinoza as a lens grinder, Blake as an engraver, Einstein as a patent examiner, for example.

In conventional schools (as in conventional society) 10,000 questions go unanswered, not only because a teacher with many students has no time to answer them, but also because most teachers wouldn't know most of the answers.

The parents of W. J. Sidis and J. S. Mill were remarkably well educated people who, because they dissented from society's ideology, chose to spend much of their time educating their children. Whenever a question about Euclidean geometry or Greek grammar occurred to the child, it could be answered immediately. It was only natural that progress would be fast, but there were more important differences.

When questions are answered, curiosity is rewarded, and the person is enlivened. In school, when following instructions and conforming to a routine is the main business, many questions must go unanswered, and curiosity is punished by the dulling emptiness of the routine.

Some schools are worse than others. For example, slum children were given I.Q. tests when they started school, and each subsequent year, and their I.Q.s dropped with each year of school. In a stimulating environment, the reverse can happen, the I.Q. can rise each year. Since the tests aren't "culture free," their scores reflected the material that they were being taught, but they undoubtedly also reflected the increasing boredom and despair of the children in a bad school, or the increasing liveliness of the children in the stimulating environment.

I have spoken with people in recent years who still held the idea of a fixed genetic mental potential, who believe that poor children fall behind because they are reaching their "genetic limit." For them, the I.Q. represents an index of intrinsic quality, and is as important as distinguishing between caviar and frogs' eggs. The rat research of Marion Diamond and others at the University of California, however, showed that the structure, weight, and biochemistry of a rat's brain changes, according to the amount of environmental stimulation and opportunity for exploration. This improvement of brain structure and function is passed on to the next generation, giving it a head-start. It isn't likely that rats are more disposed than humans to benefit from mental activity, and in the years since Diamond's research there have been many discoveries showing that brains of all

sorts complexify structurally and functionally in response to stimulation.

Rats isolated in little boxes, generation after generation--the normal laboratory rats--were the standard, but now it's known that isolation is a stress that alters brain chemistry and function.

Willy Sidis and John Stuart Mill were being stimulated and allowed to develop in one direction, but they were being isolated from interaction with their peers. When Mill was twenty he went into a depression, and later he wrote that it was because he discovered that he was unable to ***feel.*** He had developed only part of his personality.

Bertrand Russell (1872-1970), orphaned at the age of four, went to live with his grandmother, who chose not to send him to school, but provided tutors. He didn't experience a sense of academic pressure, and was able to read whatever he wanted in his late grandfather's library. He didn't realize that he was unusually bright until he went to Cambridge. The unusual freedom of his childhood must have contributed to his willingness to hold unpopular opinions. In 1916 he was fined, and in 1918 imprisoned for 6 months, for opposing the war.

In 1927, Russell and his wife, Dora Black, started a school. He later wrote that, although the average student at the school was very bright, an exceptionally bright student was likely to be ostracized by the less bright students. He commented on the harm done to the brightest students by their social isolation, probably thinking about his own education in relative isolation. A psychologist (Leta Hollingworth, 1942) has made similar observations about the isolation that can be produced by a large difference of I.Q. She did a series of studies of very bright children, beginning in 1916, including working with some of them in a program she designed in a New York public school. Her empathy allowed her to discover things that weren't apparent to her contemporaries.

During this time Lewis Terman was studying bright children, and wanted to disprove some of the popular stereotypes about intelligent people, and to support his ideology of white racial superiority. In 1922 he got a large grant, and sorted out about 1500 of the brightest children from a group of 250,000 in California. He and his associates then monitored them for the rest of their lives (described in ***Genetic Studies of Genius***). His work contradicted the stereotype of bright people as being sickly or frail, but, contrary to his expectation, there was an association between maladjustment and higher I.Q.; the incidence of neurotic fatigue, anxiety, and depression increased along with the I.Q. The least bright of his group were more successful in many ways than the most bright. He didn't really confront the implications of this, though it seriously challenged his belief in a simple genetic racial superiority of physique, intellect, and character.

I.Q. testing originated in a historical setting in which its purpose was often to establish a claim of racial superiority, or to justify sterilization or "euthanasia," or to exclude immigrants. More recently, the tests have been used to assign students to certain career paths. Because of their use by people in power to control others, the I.Q. tests have helped to create misunderstanding of the nature of intelligence. A person's "I.Q." now has very strong associations with the ideology of schooling as a road to financial success, rather than to enrichment of a shared mental life.

If a bad school resembles, on the intellectual level, a confining rat box, the educational isolation of Mill, Russell, and Sidis was emotionally limiting, almost like solitary confinement. Once when Willy Sidis was arrested for marching in a May Day parade, his father was able to keep him from going to prison, but Willy apparently would have preferred the real prison to life with his parents.

None of these three famous intellects was known for youthful playfulness, though playfulness is a quality that's closely associated with intelligence in mammals and birds. (Russell, however, in middle age developed many new interests, such as writing short stories, and had many new loves even in old age.) Stress early in life, such as isolation, reduces the playfulness of experimental animals. Playfulness is contagious, but so is the inability to play.

In schools like Summerhill, which was founded in 1921 by A. S. Neill, students aren't

required to attend classes when they would rather do something else, but at graduation they usually do better on their standardized national examinations than students who have dutifully attended classes for years. For students, as for rats, freedom and variety are good for the brain, and tedious conformity is harmful. When a school is very good, it can spread a contagion of playfulness along with an interest in learning.

An environment that fosters optimal intelligence will necessarily promote the development of emotional health, and will almost certainly foster good physical health and longevity, because no part of the physiological system can thrive at the expense of another part. And within the boundaries of life-enriching environments, there are infinite possibilities for variety.

There is a common belief in the rigidity of the adult nervous system, in analogy with feral cats or dogs, that supposedly can't be tamed if they have grown up without knowing humans. But people who have had the inclination to understand wild animals have found that, even when the animals have been captured as adults, they can become as sociable as if they had grown up in domestication. The "horse whisperer" demonstrated this sort of empathetic approach to animals. Sometimes, these people have a similar ability to communicate with people who are retarded, or autistic, or demented, but the professionalization of society has made it increasingly unlikely that people with the need for intuitive help will encounter someone who is able to give it. The closest psychology has come to professionally recognizing the importance of empathy was in Carl Rogers' work, e.g., *Client-Centered Therapy.*

Rogers showed that a sense of solidarity must exist between therapist and client for the therapy to be helpful. A similar solidarity has to exist between teacher and student, for education to be successful. If ordinary family and social contacts could occur within such an atmosphere of mutual respect, psychopathology (including learning difficulties) would be much less common.

Although three individuals don't prove an argument, I think the lives and situations of Sidis, Mill, and Russell are usefully symbolic. Sidis, who grew up under intense pressure and social isolation and in extreme poverty, died at the age of 46. Mill, who was educated mainly by his father, in secure financial circumstances, experienced social isolation and moderate pressure, and lived about 20 years longer than Sidis did. Russell, who grew up in the highest circles of the ruling class, experienced no pressure, and only the mild kind of social isolation that wasn't exceptional for his class. He lived to be 97.

The psychopathology of social isolation has been studied in a variety of animals, and many features are similar across species, including humans. Aggression, helplessness, and reduced ability to learn are typically produced in animals by social isolation, and it's clear that certain kinds of family environment produce the same conditions in children. Schools seldom help, and often hinder, recovery from such early experiences.

"Vital exhaustion," decreased slow wave sleep, and anger, which are associated with the "type A personality" and with circulatory and heart disease, appear to have their origin in childhood experiences. Low income and financial insecurity are strongly associated with anger, sleep disturbances, and circulatory disease. In animals stressed by social isolation, similar features emerge, under the influence of decreased neurosteroids, and increased serotonin and activity of the glucocorticoid system.

The "smart drug" culture has generally been thinking pharmaceutically rather than biologically. Behind that pharmaceutical orientation there is sometimes the idea that the individual just isn't trying hard enough, or doesn't have quite the right genes to excel mentally.

Many stimulants--amphetamine and estrogen, for example--can increase alertness temporarily, but at the expense of long range damage. The first principle of stimulation should be to avoid a harmful activation of the catabolic stress hormones. Light, play, environmental variety and exploratory conversations stimulate the whole organism in an integral way, stimulating repair processes and developmental processes.

Any chemical support for intelligence should take into account the mind-damaging stresses that our culture can impose, and provide defense

against those. In darkness and isolation, for example, the stress hormones increase, and the brain-protective steroids decrease. The memory improvement that results from taking pregnenolone or thyroid (which is needed for synthesizing pregnenolone from cholesterol) is the result of turning off the dulling and brain-dissolving stress hormones, allowing normal responsiveness to be restored.

If we know that rats nurtured in freedom, in an interesting environment, grow more intelligent, then it would seem obvious that we should experiment with similar approaches for children--if we are really interested in fostering intelligence. And since violence and mental dullness are created by the same social stresses, even the desire to reduce school violence might force the society to make some improvements that will, as a side effect, foster intelligence.

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John Holt, from the introduction to his book, *Teach Your Own,* (New York: Dell, 1981): "The children in the classroom, despite their rich backgrounds and high I.Q.'s, were with few exceptions frightened, timid, evasive, and self-protecting. The infants at home were bold adventurers."

"It soon became clear to me that children are by nature and from birth very curious about the world around them, and very energetic, resourceful, and competent in exploring it, finding out about it, and mastering. In short, much more eager to learn, and much better at learning, than most adults. Babies are not blobs, but true scientists. Why not then make schools into places in which children would be allowed, encouraged, and (if and when they asked) helped to explore and make sense of the world around them (in time and space) in ways that most interested them?"

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Neuroscience 2000;100(4):749-68. **Behavioral, neurochemical and endocrinological characterization of the early social isolation syndrome.** Heidbreder CA, Weiss IC, Domeney AM, Pryce C, Homberg J, Hedou G, Feldon J, Moran MC, Nelson P. "Rearing rats in isolation has been shown to be a relevant paradigm for studying early life stress and **understanding the genesis of depression and related affective disorders.** Recent studies from our laboratory point to the relevance of studying the social isolation syndrome as a function of home caging conditions."

Stroke 1991 Nov;22(11):1448-51. **Platelet secretory products may contribute to neuronal injury.** Joseph R, Tsering C, Grunfeld S, Welch KM. BACKGROUND: We do not fully understand the mechanisms for neuronal

damage following cerebral arterial occlusion by a thrombus that consists mainly of platelets. The view that certain endogenous substances, such as glutamate, may also contribute to neuronal injury is now reasonably well established. Blood platelets are known to contain and secrete a number of substances that have been associated with neuronal dysfunction. Therefore, we hypothesize that a high concentration (approximately several thousand-fold higher than in plasma, in our estimation) of locally released platelet secretory products derived from the causative thrombus may contribute to neuronal injury and promote reactive gliosis. SUMMARY OF COMMENT: We have recently been able to report some direct support for this concept. When organotypic spinal cord cultures were exposed to platelet and platelet products, a significant reduction in the number and the size of the surviving neurons occurred in comparison with those in controls. We further observed that serotonin, a major platelet product, has neurotoxic properties. There may be other platelet components with similar effect. **CONCLUSIONS: The hypothesis of platelet-mediated neurotoxicity gains some support from these recent in vitro findings. The concept could provide a new area of research in stroke, both at the clinical and basic levels.**

Am J Psychiatry 1981 Aug;138(8):1082-5. **Tryptophan metabolism in children with attentional deficit disorder.** Irwin M, Belendiuk K, McCloskey K, Freedman DX The authors present the first report, to their knowledge, of hyperserotonemia in children with attentional deficit disorder who had normal intelligence. Hyperserotonemic children had significantly lower levels of plasma total and protein-bound tryptophan and a higher percentage of free tryptophan than those with normal serotonin levels. Plasma kynurenine did not differ, suggesting that the hyperserotonemia is not due to a blockade of the kynurenine pathway but may reflect on increase in tissue tryptophan uptake and use.

J Neuropsychiatry Clin Neurosci 1990 Summer;2(3):268-74. **Autistic children and their first-degree relatives: relationships between serotonin and norepinephrine levels and intelligence.** Cook EH, Leventhal BL, Heller W, Metz J, Wainwright M, Freedman DX "Whole-blood serotonin (5-HT) and plasma norepinephrine (NE) were studied in 16 autistic children, 21 siblings of autistic children, and 53 parents of autistic children. **Both plasma NE and whole-blood 5-HT were negatively correlated with vocabulary performance."** "Eighteen subjects were hyperserotonemic (whole-blood 5-HT greater than 270 ng/ml). For these subjects, plasma NE was significantly higher than for subjects without hyperserotonemia."

Biol Psychiatry 1998 Dec 15;44(12):1321-8. **Cerebrospinal fluid monoamines in Prader-Willi syndrome.** Akefeldt A, Ekman R, Gillberg C, Mansson JE "The behavioral phenotype of Prader-Willi syndrome (PWS) suggests hypothalamic dysfunction and altered neurotransmitter regulation. The purpose of this study was to examine whether there was any difference in the concentrations of monoamine metabolites in the cerebrospinal fluid (CSF) in PWS and non-PWS comparison cases." "The concentrations of **dopamine and particularly serotonin metabolites were increased in the PWS group. The differences were most prominent for 5-hydroxyindoleacetic acid. The increased concentrations were found in all PWS cases independently of age, body mass index, and level of mental retardation." "The findings implicate dysfunction of the serotonergic system and possibly also of the dopamine system** in PWS individuals . . . ."

Pharmacol Biochem Behav 1976 Jul;5(1):55-61. **The role of serotonergic pathways in isolation-induced aggression in mice.** Malick JB, Barnett A Male mice that became aggressive following four weeks of social isolation were treated with seven known serotonin receptor antagonists. All of the **antiserotonergic drugs selectively antagonized the fighting behavior of the isolated mice; the antiaggressive activity was selective since, at antifighting doses, none of the drugs either significantly altered spontaneous motor activity** or impaired inclined-screen performance. **Antagonism of 5-HTP-induced head-twitch was used as an in vivo measure of antiserotonergic activity and a statistically significant correlation existed between potency as an antiserotonergic and potency as an antiaggressive.** PCPA, a serotonin depletor, also significantly **antagonized isolation-induced aggression** for at least 24 hr postdrug administration. The interrelationship between cholinergic and serotonergic mechanisms in the mediation of isolation aggression was investigated. The involvement of serotonergic systems in isolation-induced aggression is discussed.

Probl Endokrinol (Mosk) 1979 May-Jun;25(3):49-52 **[Role of serotonin receptors of the medial-basal hypothalamus in the mechanisms of negative feedback of the hypophyseal-testicular complex].** Naumenko EV, Shishkina GT. "Administration of serotonin into the lateral ventricle of the brain of male rats, against the background of complete isolation of the medial-basal hypothalamus was accompanied by the block of the compensatory elevation of the blood testosterone level following unilateral castration."

Encephale 1994 Sep-Oct;20(5):521-5. **[Can a serotonin uptake agonist be an authentic antidepressant? Results of a multicenter, multinational therapeutic trial].** Kamoun A, Delalleau B, Ozun M The classical biochemical hypothesis of depression posits a functional deficit in central neurotransmitter systems particularly serotonin (5-HT) and noradrenaline. The major role suggested for 5-HT in this theory led to the development of a large number of compounds which selectively inhibit 5-HT uptake. Numerous clinical trials have demonstrated the antidepressant efficacy of such types of serotoninergic agents, supporting 5-HT deficit as the main origin of depression. **Therefore, everything seemed clear: depression was caused by 5-HT deficit. Tianeptine is clearly active in classical animal models predictive of antidepressant activity, and is also active in behavioral screening tests: it antagonizes isolation induced**

aggression in mice and behavioral despair in rats. Biochemical studies have revealed that in contrast to classical tricyclic antidepressant, **tianeptine stimulates 5-HT uptake** in vivo in the rat brain. This somewhat surprising property was observed in the cortex and the hippocampus following both acute and chronic administrations. This increase in 5-HT uptake has also been confirmed in rat platelets after acute and **chronic administrations. Moreover, in humans, a study in depressed patients demonstrated that tianeptine significantly increased platelet 5-HT uptake after a single administration as well as after 10 and 28 days of treatment. The antidepressant activity of tianeptine has been evaluated in controlled studies versus reference antidepressants. Another study aiming to compare the antidepressant efficacy of tianeptine versus placebo and versus imiporamine is** presented. 186 depressed patients were included in this trial. They presented with either Major Depression, single episode (24.6%) or Major Depression recurrent (66.8%) or Bipolar Disorder (depressed) (8.6%).

Psychopharmacology (Berl) 1998 Oct;139(3):255-60. **Ca2+ dependency of serotonin and dopamine release from CNS slices of chronically isolated rats.** Jaffe EH. "We have used chronic isolated housing as an animal model of depression." "The following questions were addressed: first, if there is a change in the depolarization dependent release of DA and 5-HT from these CNS structures, and second, if the release is through the classical exocytotic mechanism. **A significant increase in KCl stimulated release of 5-HT was observed in chronically isolated animals when compared to controls.** 5-HT release was completely abolished from controls or isolated animals, when slices were incubated with Krebs containing zero Ca2+/10 mM Mg2+, the inorganic Ca2+ channel blockers, Cd2+ or Ni2+ and the calmodulin inhibitor, trifluoperazine." **"The basal release of DA and 5-HT was similar in control and isolated animals and was not affected by the Ca2+ channel antagonists. The results suggest that extracellular Ca2+-dependent release of 5-HT and, to a lesser degree, of DA, is increased in this chronic animal model of depression in** several CNS structures."

Gen Pharmacol 1994 Oct;25(6):1257-1262. **Serotonin-induced decrease in brain ATP, stimulation of brain anaerobic glycolysis and elevation of plasma hemoglobin; the protective action of calmodulin antagonists.** Koren-Schwartzer N, Chen-Zion M, Ben-Porat H, Beitner R Department of Life Sciences, Bar-Ilan University, Ramat Gan, Israel. **1. Injection of serotonin (5-hydroxytryptamine) to rats, induced a dramatic fall in brain ATP level, accompanied by an increase in P(i). Concomitant to these changes, the activity of cytosolic phosphofructokinase, the rate-limiting enzyme of glycolysis, was significantly enhanced. Stimulation of anaerobic glycolysis was also reflected by a marked increase in lactate content in brain. 2. Brain glucose** 1,6-bisphosphate level was decreased, whereas fructose 2,6-bisphosphate was unaffected by serotonin. 3. All these serotonin-induced changes in brain, which are characteristic for cerebral ischemia, were prevented by treatment with the calmodulin (CaM) antagonists, trifluoperazine or thioridazine. **4. Injection of serotonin also induced a marked elevation of plasma hemoglobin, reflecting lysed erythrocytes,** which was also prevented by treatment with the CaM antagonists. 5. **The present results suggest that CaM antagonists may be effective drugs in treatment of many pathological conditions and diseases in which plasma serotonin levels are known to increase.**

Gen Pharmacol 1994 Oct;25(6):1257-1262. **Serotonin-induced decrease in brain ATP, stimulation of brain anaerobic glycolysis and elevation of plasma hemoglobin; the protective action of calmodulin antagonists.** Koren-Schwartzer N, Chen-Zion M, Ben-Porat H, Beitner R Department of Life Sciences, Bar-Ilan University, Ramat Gan, Israel. **1. Injection of serotonin (5-hydroxytryptamine) to rats, induced a dramatic fall in brain ATP level, accompanied by an increase in P(i). Concomitant to these changes, the activity of cytosolic phosphofructokinase, the rate-limiting enzyme of glycolysis, was significantly enhanced. Stimulation of anaerobic glycolysis was also reflected by a marked increase in lactate content in brain. 2. Brain glucose** 1,6-bisphosphate level was decreased, whereas fructose 2,6-bisphosphate was unaffected by serotonin. 3. All these serotonin-induced changes in brain, which are characteristic for cerebral ischemia, were prevented by treatment with the calmodulin (CaM) antagonists, trifluoperazine or thioridazine. 4. Injection of serotonin also induced a marked elevation of plasma hemoglobin, reflecting lysed erythrocytes, which was also prevented by treatment with the CaM antagonists. 5. The present results suggest that CaM antagonists may be effective drugs in treatment of many pathological conditions and diseases in which plasma serotonin levels are known to increase.

J Neural Transm 1998;105(8-9):975-86. **Role of tryptophan in the elevated serotonin-turnover in hepatic encephalopathy.** Herneth AM, Steindl P, Ferenci P, Roth E, Hortnagl H. "The increase of the brain levels of 5-hydroxyindoleacetic acid (5-HIAA) in hepatic encephalopathy (HE) suggests an increased turnover of serotonin (5-HT)." "These results provide further evidence for the role of tryptophan in the elevation of brain 5-HT metabolism and for a potential role of BCAA in the treatment of HE."

Tugai VA; Kurs'kii MD; Fedoriv OM. **[Effect of serotonin on Ca2+ transport in mitochondria conjugated with the respiratory chain].** Ukrainskii Biokhimicheskii Zhurnal, 1973 Jul-Aug, 45(4):408-12.

Kurskii MD; Tugai VA; Fedoriv AN. **[Effect of serotonin and calcium on separate components of respiratory chain of mitochondria in some rabbit tissues].** Ukrainskii Biokhimicheskii Zhurnal, 1970, 42(5):584-8.

Watanabe Y; Shibata S; Kobayashi B. **Serotonin-induced swelling of rat liver mitochondria.** Endocrinologia Japonica, 1969 Feb, 16(1):133-47.

Mahler DJ; Humoller FL. **The influence of serotonin on oxidative metabolism of brain mitochondria.**

Proceedings of the Society for Experimental Biology and Medicine, 1968 Apr, 127(4):1074-9.

Eur J Pharmacol 1994 Aug 11;261(1-2):25-32. **The effect of alpha 2-adrenoceptor antagonists in isolated globally ischemic rat hearts.** Sargent CA, Dzwonczyk S, Grover G.J. "The alpha 2-adrenoceptor antagonist, yohimbine, has been reported to protect hypoxic myocardium. Yohimbine has several other activities, including 5-HT receptor antagonism, at the concentrations at which protection was found." "Pretreatment with yohimbine (1-10 microM) caused a concentration-dependent increase in reperfusion left ventricular developed pressure and a reduction in end diastolic pressure and lactate dehydrogenase release. The structurally similar compound rauwolscine (10 microM) also protected the ischemic myocardium. In contrast, idozoxan (0.3-10 microM) or tolazoline (10 microM) had no protective effects. The **cardioprotective effects of yohimbine were partially reversed by 30 microM 5-HT. These results indicate that the mechanism for the cardioprotective activity of yohimbine may involve 5-HT receptor antagonistic activity."**

Zubovskaia AM. **[Effect of serotonin on some pathways of oxidative metabolism in the mitochondria of rabbit heart muscle].** Voprosy Meditsinskoi Khimii, 1968 Mar-Apr, 14(2):152-7.

Warashina Y. **[On the effect of serotonin on phosphorylation of rat liver mitochondria**]. Hoppe-Seylers Zeitschrift fur Physiologische Chemie, 1967 Feb, 348(2):139-48.

Eur Neuropsychopharmacol 1997 Oct;7 Suppl 3:S323-S328. **Prevention of stress-induced morphological and cognitive consequences.** McEwen BS, Conrad CD, Kuroda Y, Frankfurt M, Magarinos AM, McKittrick C. Atrophy and dysfunction of the human hippocampus is a feature of aging in some individuals, and this dysfunction predicts later dementia. There is reason to believe that adrenal glucocorticoids may contribute to these changes, since the elevations of glucocorticoids in Cushing's syndrome and during normal aging are associated with atrophy of the entire hippocampal formation in humans and are linked to deficits in short-term verbal memory. We have developed a model of stress-induced atrophy of the hippocampus of rats at the cellular level, and we have been investigating underlying mechanisms in search of agents that will block the atrophy. Repeated restraint stress in rats for 3 weeks causes changes in the hippocampal formation that include suppression of 5-HT1A receptor binding and atrophy of dendrites of CA3 pyramidal neurons, as well as impairment of initial learning of a radial arm maze task. **Because serotonin is released by stressors and may play a role in the actions of stress on nerve cells, we investigated the actions of agents that facilitate or inhibit serotonin reuptake.** Tianeptine is known to enhance serotonin uptake, and we compared it with fluoxetine, an inhibitor of 5-HT reuptake, as well as with desipramine. **Tianeptine treatment (10 mg/kg/day) prevented the stress-induced atrophy of dendrites of CA3 pycamidal neurons,** whereas neither fluoxetine (10 mg/kg/day) nor desipramine (10 mg/kg/day) had any effect. **Tianeptine treatment also prevented the stress-induced impairment of radial maze learning.** Because **corticosterone- and stress-induced atrophy of CA3 dendrites is also blocked by phenytoin, an inhibitor of excitatory amino acid release and actions, these results suggest that serotonin released by stress or corticosterone may interact pre- or post-synaptically with glutamate released by stress or corticosterone, and that the final common path may involve interactive effects between serotonin and glutamate receptors on the dendrites of CA3 neurons innervated by mossy fibers from the dentate gyrus. We discuss the implications of these findings for treating cognitive impairments and the risk for dementia in the elderly.**

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Ray Peat's Newsletter

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"Cocaine babies," criminal responsibility, and medicine

In the 1950s and later, the US medical establishment was still arguing for the safety of prenatal x-rays.

Through the 1950s and 1960s the U.S Atomic Energy Commission and the medical profession collaborated in keeping the public from knowing the dangers of prenatal exposures to harmful influences, including drugs, diet, and radiation. Childhood cancer and brain defects were produced in millions of children as a result. Fetotoxic drugs are still in use by physicians.

The problem is, partly, that medicine is not a biological science. It is a profession, meaning that whatever it professes to know has the legal status of truth.

Problem-centered ecological health education would be a step toward solution of the problems of public health.

Many pregnant women have been prosecuted for "delivering an illegal drug to their fetus" when they use cocaine.

If a person chooses to believe something that's contrary to the best evidence, when they are aware of the evidence, that can be called faith. But when their behavior harms others, their willful ignorance becomes a moral issue.

When the medical profession starts to get something right, a century after researchers had clarified the facts, the general euphoria should be tempered by what is actually happening. The medical profession is now concerned about the harmful effects of using cocaine and alcohol in pregnancy. Exactly what does this new seemingly realistic attitude mean? What could motivate this great new interest in the well-being of the fetus? Why are these substances the focus of such concern? I'm afraid it is purely because these are all self-administered substances, and the blame can be placed on the user, rather than on any powerful institutions.

Just 30 years ago, the conventional wisdom was that the fetus is isolated and insulated from the mother's metabolism. The thalidomide episode was already forcing doctors to acknowledge that ***some*** drugs might get through the placenta, though the drug industry was reluctant to lose the pregnant-woman market.

"The legal responses to the "crack baby scare" clearly did much more harm than good to both the mothers and the children. Making substance abuse during pregnancy a crime kept mothers from prenatal medical care, thereby endangering the fetus far more than would be the case with drug use, and discouraged them from seeking drug treatment."

". . . the fact remains that recent studies on cocaine use by pregnant women clearly demonstrate that the pharmacological impact of cocaine has been greatly exaggerated, that many other factors impact on fetal and newborn development, and that legal responses to maternal cocaine use have made every aspect of the problem worse."

Gary Potter
Professor, Police Studies
Eastern Kentucky University

The idea that fetal damage could result from the mother's malnutrition was rejected as an impossibility. The food industry didn't want to have to test their GRAS (generally recognized as safe) additives for fetal safety, and it didn't want women to get the idea that they should avoid junk foods, such as pasta and bread, during pregnancy. People at the Harvard School of Public Health said that it was nonsense to think that foods could

be nutrient-deficient--"if the soil doesn't have the chemicals plants need, the plants won't grow; therefore, all crops are fully nutritious." The chemical composition of plants was supposedly determined strictly by their genes, so the soil couldn't determine their nutrient content. The fetus, like a plant, was supposed to be genetically determined, but unlike a plant, it was said to live like a parasite on the mother, taking everything it needs from the mother's tissues, rather than from the mother's dietetic intake. If the mother was alive, her nutritional condition couldn't have anything to do with the fetus.

Probably in reaction against the biological evidence that maternal malnutrition produced defective offspring, the American medical establishment adopted the concept that "fetal malnutrition" existed, and was caused by a defective uterus or placenta, not by anything the mother might have eaten or failed to eat. In Italy and Germany in the 1970s, a slightly saner concept was emerging, in which it was proposed that a malnourished fetus could be fed by infusing amino acids into the amniotic fluid, or that the mother and fetus might benefit from intravenous glucose and amino acids. The use of progestins to stimulate placental development was also suggested in Europe. (Farad and Picas, 1976.)

Poor, illiterate, drug using women are now being charged with "giving cocaine to their fetus" when they use the drug. What this means is that there are elements in our judicial system which are saying that illiterates and derelicts must be held to a higher standard than doctors of medicine were when these women were children--and to a higher standard than that of the present state licensing boards which have nothing to say to physicians who prescribe reducing diets and diuretics and teratogenic drugs, and even x-rays, to pregnant women.

Several articles on cocaine babies have emphasized the huge cost resulting from their health care. I have never seen a discussion of the economics of the damage caused by medical and governmental aggressions against the public. If the cost to the public of caring for cocaine babies is the important issue, then we should consider the cost of preventing the damage in the most direct way, but that requires knowing what the real causes of the damage are.

The evidence that these babies' defects are caused by cocaine is fairly odd. Being scientifically careful about evaluating the evidence in this situation is important, considering the history and the context.

In the late 1960s, most of the publications on the dangers of LSD and marihuana were fraudulent. While typical LSD users took about 100 micrograms of the drug, experiments using doses that were the human equivalent of tens of thousands of micrograms were used to argue for the drug's dangers. Those doses would have killed people, in a short time.

In humans, as little as 20 milligrams of cocaine injected intravenously is said to have been fatal, and the average lethal ***oral*** dose is 500 milligrams. Injected cocaine is much more powerful than oral doses. **In animal studies, doses equivalent to thousands of milligrams per day in humans are injected into rats before harmful effects are seen in the fetuses.** Drugs injected intravenously or injected into the peritoneal cavity are very rapidly and completely absorbed, and the only doses that caused measurable fetal harm in rats were doses that, on a weight basis, almost certainly would have caused nearly instantaneous death in humans.

Cocaine suppresses appetite. When pregnant animals are fed the same limited amount of food consumed by cocaine-treated animals, their undernourished offspring show most of the same effects seen in the litters that were exposed to cocaine.

The human placenta passes a smaller percentage of cocaine to the fetus than the rat placenta does, and the liver of the human fetus is more effective at detoxifying cocaine, so any effects of cocaine on rat fetuses are probably going to be larger than any effect on the human fetus.

Behavioral disturbances in the offspring are considered to be a very sensitive indicator of a chemical's teratogenicity, but some researchers have concluded that cocaine might not be a behavioral teratogen. (Riley and LaFiette, 1996) Others have described it as "not a potent neuroteratogen." (Chen, et al., 1996)

The effects of cocaine that are supposedly seen in humans seem not to be produced by cocaine in lab animals. Intrauterine growth retardation, microencephaly, abruptio placentae, spontaneous abortion, sudden infant death syndrome, and mental retardation are commonly said to be the consequences of prenatal exposure to cocaine. Many things can contribute to those problems, but malnutrition is the most common cause, and is the one that American medicine goes to great lengths to avoid mentioning. Prenatal x-rays, diuretics, and pregnancy weight-control diets are other important causes.

How is it that cocaine and starvation can produce the same symptoms? I think the evidence indicates that cocaine isn't the cause of the pregnancy problems that are blamed on it. But, since cocaine suppresses the appetite, it does have some role in the problems of gestation caused by malnutrition.

Most crack smokers are poor, very few eat well, and nearly all of them smoke. Smoking causes damage to the fetus that is much easier to demonstrate than the theoretical damage caused by cocaine. The media are filled with the cocaine-baby issue. "Have you ever seen a cocaine baby?" But do we hear them asking "Have you ever seen a baby born to a smoker?" Or, "have you seen the babies of malnourished women?"

To pretend that any effects produced in pregnant rats, by a dose of cocaine which is many times larger on a weight basis than the supposedly lethal human dose, are relevant to public health, is crude propaganda, and presumably has the purpose of supporting political, judicial or military actions that are completely unrelated to public health or morality.

Putting the medico-legal propaganda in its best light, it is scientifically atrocious. But the actual moral issue is that it is not used for any constructive purpose. One nutritious high protein meal every day would probably solve the "cocaine baby problem," but it appears that neither the government nor the medical establishment is interested in solving the problem.

Novocaine (procaine) was introduced as a substitute for cocaine, but it has been found to have protective effects on the organism, as an adaptogen. Lidocaine and other local anesthetics have many important protective effects. In this context, some experiments that hint at a fetus-*protecting* effect of cocaine deserve further investigation.

Cocaine was displaced from medical use, first by the proprietary synthetic local anesthetics, and then, in the 1930s, by the proprietary amphetamines.

As a stimulant, cocaine increases the metabolic rate, which in turn can lead to the wastage of protein, to provide energy. Conventional first aid for a cocaine overdose includes providing glucose and thiamine, to provide energy. The same nutritional support, but preferably with additional protein, is obviously appropriate for protection of the fetus. The presence of increased amounts of ammonia in the urine indicates malnutrition in both adults and newborns, and might be a useful indicator for nutritionally stressed pregnancies. Supplementing both dietary protein and carbohydrate might be the simplest treatment for many types of gestational stress, including preeclampsia and "recreational" cocaine use.

The Andean people who use coca regularly appear to suffer no harmful effects. Coca chewing prevents the hypoglycemia that can be produced by extremely high altitude. It is common to keep a wad of the leaf in the mouth all day. The dental health of coca-chewers is so good that a Bolivian company has marketed a toothpaste containing coca leaf. (But it is probably the high altitude itself that is mainly responsible for their good teeth.) The coca leaf has been used medicinally in South America for improved fertility, prolongation of virility into old age, prevention of altitude sickness, and various other purposes. The association of coca chewing in these cultures with magic and gods with erect phalluses (*El Tio, Supay*) probably affected the herb's treatment by the anti-erotic cultures.

At very high altitude, fertility is limited by the availability of oxygen. Altitude itself tends to increase the ratio of progesterone to estrogen, as a protective adaptation involving increased carbon dioxide in the tissues. Cocaine increases the production of the pituitary gonadotrophin, LH

(luteinizing hormone), which increases ovarian progesterone production. In men, LH increases testosterone production. Chewing coca leaves has been found to sharply increase the amount of progesterone in saliva. Increased progesterone would increase the ability to maintain pregnancy under stressful conditions.

Used moderately, for health purposes, there would seem to be no problem with cocaine, and there seems to be a physiological rationale even for its use during pregnancy under some conditions. The use of progesterone, thyroid, and nutrition would obviously be better ways to protect fetal development.

Smoking during pregnancy is a much bigger public health issue than cocaine use. Ranking with smoking, in terms of damage done to developing babies, are prescribed diuretics, inappropriate drugs for epilepsy during pregnancy, weight-control diets for pregnant women, x-rays of the developing fetus, and--probably the biggest problem of all--poverty and malnutrition.

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J Reprod Med 1974 Nov;13(5):170-4 **Prevention of gestational failure by high protein diet.** Grieve JF.

Am J Perinatol 1989 Jan;6(1):4-7. **Increased neonatal urinary ammonia: a marker for in utero caloric deprivation?** Wolfe HM, Sokol RJ, Dombrowski MP, Bottoms SF, Norman GS. **The decline in the urinary urea to ammonia ratio represents a simple measure of nutritional status in the adult.** We examined the relationship of this ratio to nutrient-related fetal growth retardation. Levels of ammonia and urea nitrogen were measured in the first voided urine and cord blood from 15 term infants exhibiting a wide range of growth. Analysis by multiple regression with neonatal ponderal index as the primary dependent variable revealed a significant correlation between lowered ponderal index and decreased urinary urea and ammonia. **The correlation was primarily a function of increasing ammonia levels,** with no relationship between fetal leanness and urinary urea. Comparable cord artery and vein ammonia **suggest that placental ammoniagenesis was not a major determinant** of observed elevations in urinary ammonia. **Confirmation of the striking correlation between increased urinary ammonia and lowered neonatal ponderal index may afford a simple test for the identification of nutrient-related growth retardation.**

Eur J Clin Nutr 1989;43 Suppl 1:19-25. **Amino acid availability and brain development: effects of nutritional and metabolic inadequacies.** Huether G.

Teratology 1996 Mar;53(3):145-51. **Cocaine exposure during the brain growth spurt failed to produce cerebellar Purkinje cell loss in rat pups.** Chen WJ, McAlhany RE Jr, Maier SE, West JR.

Acta Diabetol 1994 Sep;31(3):141-6. **Embryonic growth impaired by maternal hypoglycemia during early organogenesis in normal and diabetic rats.** Kawaguchi M, Tanigawa K, Tanaka O, Kato Y. **"Maternal hypoglycemia lowered the DNA content in normal but not diabetic embryos . . . ."**

Pharmacol Biochem Behav 2000 Jun;66(2):449-53. **Cocaine affects progesterone plasma levels in female rats.** Quinones-Jenab V, Perrotti LI, Ho A, Jenab S, Schlussman SD, Franck J, Kreek MJ. "Female Fischer rats injected with cocaine in a "binge" pattern (15 mg/kg, IP, three times a day, at 1-h intervals) for 1 day had significantly higher levels of progesterone than saline-treated controls ($p < 0.001$)." **"Progesterone plasma levels were also increased after a single dose of cocaine (15 mg/kg)."** "Thus, acute cocaine induced increases in progesterone plasma levels in intact female rats are probably due to an increase in secretion rates of progesterone rather than an acceleration of its biotransformation."

Obstet Gynecol 1994 Apr;83(4):613-5. **Estrogen mediates the pregnancy-enhanced cardiotoxicity of cocaine in the isolated perfused rat heart.** Kurtzman JT, Thorp JM Jr, Spielman FJ, Perry S, Mueller RA, Cefalo RC.

Am J Phys Anthropol 1993 Dec;92(4):539-44 **Brief communication: effect of coca-leaf chewing on salivary progesterone assays.** Vitzthum VJ, von Dornum M, Ellison PT

J Pharmacol Exp Ther 1993 Aug;266(2):804-11 **Acute effects of cocaine on anterior pituitary hormones in male and female rhesus monkeys.** Mello NK, Sarnyai Z, Mendelson JH, Drieze JM, Kelly M. **"Cocaine (0.8 mg/kg) stimulated a significant increase in luteinizing hormone (LH) within 10 to 20 min ($P < .01$) and LH reached peak levels (59-60% above base line) within 30 min after cocaine administration in both males and females.** Plasma cocaine levels averaged 289 +/- 23 and 346 +/- 73 ng/ml at 10 min after i.v. cocaine (0.8 mg/kg) administration in males and females, respectively. **Follicle stimulating hormone levels were**

unchanged in midluteal females. Male testosterone increased by 50% above average base-line levels 50 min after the LH peak (80 min postcocaine). These data are consistent with our previous findings that cocaine increased LH and enhanced luteinizing hormone-releasing hormone-stimulated LH in early follicular females."

J Pharmacol Exp Ther 1998 Jun; 285(3):931-45. **Fetal nicotine or cocaine exposure: which one is worse?** Slotkin TA.**"Despite extensive adverse publicity, tobacco use continues in approximately 25% of all pregnancies in the United States, overshadowing illicit drugs of abuse, including cocaine. The societal cost of maternal smoking is seen most readily in underweight newborns, in high rates of perinatal morbidity, mortality and Sudden Infant Death Syndrome and in persistent deficits in learning and behavior." "In light of the fact that nearly all crack cocaine users smoke cigarettes, the identification of specific developmental effects of cocaine may prove difficult to detect. Although scientists and the public continue to pay far more attention to fetal cocaine effects than to those of nicotine or tobacco use, a change of focus to concentrate on tobacco could have a disproportionately larger impact on human health.**

NIDA Res Monogr 1996;164:53-77. **The effects of prenatal cocaine exposure on subsequent learning in the rat.** Riley EP, LaFiette MH. "The evidence provided by Spear and colleagues (1989a, 1989b), however, indicates that this deficit is relatively transitory and is not found in animals after perhaps 15 days . . . . " "The available evidence would appear to indicate that significant, biologically meaningful deficits on these tasks are not found over a wide range of doses. There are a number of reasons for these failures to find effects."

Acta Obstet Gynecol Scand 1979;58(1):37-40. **Perinatal death due to abruptio placentae in an African city.** Naeye RL, Tafari N, Marboe CC Abruptio placentae was a common cause of perinatal death in Addis Ababa, Ethiopia in 1974-1975 with a frequency of 5.5/1000 births. This disorder had its peak frequency at term. No abnormalities were found in the placentas to explain the placental abruptions but there were other clues to their genesis. There was **a strong association of the fatal abruptions with severe poverty in the mothers. These poor mothers were both undernourished and malnourished during pregnancy.** Their fetuses and neonates who died had multiple evidences of undernutrition including a relative undergrowth of adrenals, spleens and livers and a relative acceleration of lung maturation. These findings support observations in more prosperous nations that poor nutrition of the gravida may have an important role in the genesis of abruptio placentae.

S Afr Med J 1988 Jul 16;74(2):53-4. **Influence of perinatal care on stillbirths in patients of low socio-economic class.** de Jong G, Pattinson RC, Odendaal HJ. In a series of 12,587 deliveries in patients of low socio-economic class, there were 356 stillbirths; prospective analysis of these showed that 42.1% occurred in the 4.7% of cases in which the mother had received no antenatal care. When booked and unbooked patients were compared it was found that the rate of stillbirths due to infection and anoxia was significantly higher among unbooked patients, who also accounted for more intra-uterine deaths due to abruptio **placentae and congenital abnormalities. We speculate that diet and nutrition might play a major part in the causation of these intra-uterine deaths.**

Am J Obstet Gynecol 1977 Aug 1;128(7):740-6. **Abruptio placentae and perinatal death: a prospective study.** Naeye RL, Harkness WL, Utts J. "The decidual necrosis was correlated with maternal cigarette smoking and **low pregnancy weight gains** in the abruption placentae cases. The fetuses and neonates who died had a pattern of growth retardation characteristic of antenatal undernutrition, indicating that poor maternal nutrition during pregnancy may have contributed to the genesis of the abruptio placentae."

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hemorrhages. Despite suppression of maternal weight gain, **there was preservation of fetal weights at cocaine doses up to and including 80 mg/kg/day, suggesting some protection of fetal growth."**

Am J Perinatol 1989 Jan;6(1):4-7. **Increased neonatal urinary ammonia: a marker for in utero caloric deprivation?** Wolfe HM, Sokol RJ, Dombrowski MP, Bottoms SF, Norman GS. **The decline in the urinary urea to ammonia ratio represents a simple measure of nutritional status in the adult.** We examined the relationship of this ratio to nutrient-related fetal growth retardation. Levels of ammonia and urea nitrogen were measured in the first voided urine and cord blood from 15 term infants exhibiting a wide range of growth. Analysis by multiple regression with neonatal ponderal index as the primary dependent variable revealed a significant correlation between lowered ponderal index and decreased urinary urea and ammonia. **The correlation was primarily a function of increasing ammonia levels,** with no relationship between fetal leanness and urinary urea. Comparable cord artery and vein ammonia **suggest that placental ammoniagenesis was not a major determinant** of observed elevations in urinary ammonia. **Confirmation of the striking correlation between increased urinary ammonia and lowered neonatal ponderal index may afford a simple test for the identification of nutrient-related growth retardation.**

Teratology 1996 Mar;53(3):145-51. **Cocaine exposure during the brain growth spurt failed to produce cerebellar Purkinje cell loss in rat pups.** Chen WJ, McAlhany RE Jr, Maier SE, West JR.

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Am J Epidemiol 1996 Dec 15; 144(12): 1155-60. **Parental recreational drug use and risk for neural tube defects.** Shaw GM, Velie EM, Morland KB. **"Periconceptional maternal use of cocaine (odds ratio (OR) = 0.74, 95% confidence interval (CI) 0.40-1.4). . . ."** "Risks were not substantially altered after adjustment for maternal age, race/ethnicity, vitamin use, education, and household income. Increased NTD risk was also not generally associated with paternal drug use. The authors could not discern whether the decreased risks observed for these maternal exposures reflected a true association or were due to reporting bias, a disproportionate number of drug-exposed NTD cases among spontaneous abortuses that could not be ascertained, or some other bias."

Neurotoxicol Teratol 1988 Jan-Feb;10(1):51-8 **Dose-dependent consequences of cocaine on pregnancy outcome in the Long-Evans rat.** Church MW, Dintcheff BA, Gessner PK. "Despite treatment during the major periods of organogenesis and brain development, few congenital abnormalities were observed. There were, however, dose-dependent effects on maternal weight gain, maternal food and water consumption, fetal weight, maternal and fetal fatalities, fetal edema, abruptio placentae and cephalic hemorrhages. Despite suppression of maternal weight gain, there was preservation of fetal weights at cocaine doses up to and including 80 mg/kg/day, suggesting some protection of fetal growth."

Teratology 1996 Mar;53(3):145-51. **Cocaine exposure during the brain growth spurt failed to produce cerebellar Purkinje cell loss in rat pups.** Chen WJ, McAlhany RE Jr, Maier SE, West JR. "Previous studies in our laboratory indicated that cocaine exposure during the brain growth spurt period, a developmental stage vulnerable to various teratogens, did not produce microencephaly (gross brain weight measures)." "The failure of **cocaine to produce significant Purkinje cell loss (present finding) or microencephaly (previous finding) odds to the evidence indicating that cocaine is not a potent neuroteratogen."**

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Ray Peat's Newsletter

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PREMISES FOR AN ARGUMENT:

Environmental factors, including polyunsaturated fats, exogenous estrogens, and heavy metals, and nutritional deficiencies, create an exaggerated estrogenic state, which synergizes with other intermittent stresses. These external stressors provoke the release of many kinds of stress mediating signal substances.

Aging is a progressive inflammatory state, in which there is an imbalance between excitatory and restorative processes, that progresses toward a shock-like state.

The antistress hormone, cortisol, causes tissue atrophy and cellular death in the process of resisting chronic stress.

Circulation and metabolism influence each other, with inflammation and shock, hypoxic metabolism and hypoperfusion promoting each other.

Inflammatory mediators damage mitochondrial respiration and cause cell swelling. Swelling impairs circulation and cell function.

Inflammatory autoimmune diseases and diabetes are much more common in women than in men. Insulin resistance appears at puberty, and diabetes is more common in girls than in boys. At menopause, 50% of women have distinct insulin resistance. Insulin resistance and the inflammatory autoimmune diseases are clearly promoted by estrogen.

The chronic increase of cortisol in response to stress increases estrogen.

Changing metabolism, producing lactate rather than carbon dioxide, changes the pH of the cell and its water content, allowing water-soluble metals to enter mitochondria.

Diabetes, neuropathies, myopathies, schizophrenias, the degenerative brain diseases, congestive heart failure, multiple organ failure, reduced lung function, insomnia, nocturnal cramps, and many other disorders have similar metabolic features, justifying similar therapies.

Estrogen, calcium, heavy metals, and nerve degeneration.

In the 1960s, someone noticed that a certain crease on the ear-lobe was a strong indicator of the tendency to have a heart attack. A little later, different researchers showed an association of wrinkled skin with smoking, and a strong association between the percentage of polyunsaturated oils in the diet and premature wrinkling. At the same time, people were demonstrating that many factors contributed to the stiffening of connective tissues, and to a generalized "fibrosis." Intuitively, everyone seems to know that the state of the skin is an indicator of general vitality or decrepitude. But the habit of thinking in terms of specific diseases, rather than general processes, has kept people from seeing that wrinkles, and other connective tissue changes, are deeply related to the major diseases of aging.

The senile brain accumulates a variety of mineral deposits, and the argument has been made that dietary aluminum is the cause of Alzheimer's disease. It would be good to eliminate added aluminum from our public water systems and from our foods, but there is good evidence that other processes are behind the accumulation of aluminum and other minerals in our tissues.

With aging, minerals such as calcium, iron, aluminum, cadmium, lead, mercury, fluoride, uranium, etc., accumulate in animal tissues, especially when those tissues are metabolically defective. But as the soft tissues mineralize, the bones and teeth demineralize. In both hard and soft tissues, mitochondria regulate mineralization.

Mercury has been used medically for a long time, and one of the popular uses for mercurial compounds has been as a diuretic. The mercurial

diuretics suppress the kidneys' respiratory activity and their ability to retain minerals, allowing fluids to pass through them relatively unconstrained. This led to the understanding that the mercury acted by interfering with the sulfhydryl groups (mostly the cysteines in proteins) in kidney cells, so when microscopic studies showed that the mercurial diuretic caused calcification, beginning in the mitochondria, this added to knowledge of how mitochondria work, as well as to the general process of soft tissue mineralization.

Hans Selye studied the process of metal-induced calcification in rats. In one group of experiments, he showed that an excess of iron causes calcification of areas of skin that have been slightly injured, for example by having the hair plucked. Treatment of the rats with vitamin E blocked the oxidative effects of iron and prevented calcification. Ordinary injuries, such as bruises, sometimes calcify, presumably under the influence of hemoglobin and iron.

Many toxins that oxidize the sulfhydryl (SH) groups in mitochondria synergize with calcium overload to produce metabolic inactivation of the mitochondria, usually accompanied by swelling. For many years it has been recognized that a practically instantaneous effect of estrogen is to cause cells to take up water. Its next step is to stimulate the synthesis of fats. Both of these processes involve pervasive changes in the energetic processes of the cells. Among the later changes produced by estrogen is increased collagen production.

It has long been recognized that injury or irritation is likely to lead to calcification, through the stages of inflammation, edema, and fibrosis, sometimes with fatty degeneration. These are the changes that led people to think of radiation damage as a form of accelerated aging. X-ray treatment commonly causes calcification of important organs such as the brain and the heart, though skin calcification was among the first radiation side-effects noticed. After 100 years of relative scientific inertia, there has recently been some progress in understanding the common processes behind "injury induced mineralization."

The biochemical arguments in the next few paragraphs simply outline some of the facts that have been omitted from the mainstream discussions of brain aging, estrogen, and mineralization.

When I began studying the physiology of estrogen, I found that the biochemical changes it caused were the same as those of aging, oxygen-deprivation, and radiation injury.

In my experiments, I found that both aging and estrogen stimulation caused a great increase in the availability of reactive electrons, which I measured by their reaction with a dye. These electrons come from an interactive system that involves the proteins (cysteine) and glutathione, and the various cofactor-catalysts such as ascorbic acid and NADH (NAD is nicotinamide adenine dinucleotide; the name reveals its connections to the vitamin, niacin/nicotinamide, and to the "energy molecule," ATP, adenosine triphosphate, but biochemists are seldom concerned with those links; the H indicates the reduced, electronically energized form of the molecule).

Glutathione and other antioxidants tend to prevent oxidative damage to the mitochondria's sulfhydryl groups. Simply lowering the pH is highly protective against oxidative attack by metals, and this is partly because the electrons of the sulfhydryl groups are less accessible to the oxidants in an acidic environment. The formation of carbon dioxide is the fundamental process for keeping mitochondrial pH low.

Glutathione depends on being regenerated by the reducing molecule, NADH. When NADH is consumed elsewhere at a high rate, glutathione itself becomes oxidized and unable to protect the mitochondria, and the consumption of NADH (as in the formation of lactic acid) tends to consume protons, raising the pH. So the rate at which NADH is consumed can be crucial in the life and health of a cell. NAD is so closely related to the availability of ATP that the cell death system can be triggered by a deficiency of NAD (Catisti, et al., 1999).

The cell's reductive system, centering on NADH and NADPH (the extra P, phosphate, in this molecule allows it to be regulated separately from NAD), is closely involved in fat synthesis. If estrogen serves as a redox (reduction and oxidation) link between NADH and NADP, fat

synthesis will be an additional drain on the available NADH.

In the 1950s, several endocrinologists gathered evidence to show that estrogen can function as a catalyst in the oxidation and reduction of the pyridine nucleotides, NADPH and NADH. But in the 1960s, the doctrine that estrogen's effects were mediated exclusively by the "estrogen receptor" began replacing all other ideas about estrogen chemistry and physiology.

J. G. Liehr, and a few others, are still demonstrating that estrogen can function as a catalyst in "redox cycling" (alternate reduction and oxidation), which generates toxic free radicals, and can potentially serve as a drain on the NADH systems. In functioning as a redox catalyst, estrogen oscillates between an oxidized and a reduced molecular form. In this context, the ratio of the different forms of estrogen takes on an entirely different meaning than simply their different effects on the so-called estrogen receptors. Since the doctrine of the estrogen receptor became a medical preoccupation, most attention has been given to estradiol, since it is the "strongest" estrogen in some tests, though estrone, the oxidized form, is usually present in the blood in much larger quantities. The quantity of the oxidized form of estrogen is increased in certain degenerative conditions, such as uterine cancer, which is a strong argument against the idea that, as a "weaker estrogen," it would moderate the effect of estradiol.

In my dissertation, I gave a few other arguments regarding the wasteful consumption of NADH. There is now good evidence for the existence of estrogen-stimulated extramitochondrial NADH oxidases, in addition to the NADH oxidase function of age pigment, that I have discussed in an earlier newsletter.

Until the late 1970s, the fact that estrogen causes increased absorption of calcium was offered as proof that it prevents osteoporosis, but then it turned out that the increased retention of calcium was occurring ***only in the soft tissues,*** where calcification is a normal trend with aging. In fact, bone loss begins in a woman's twenties, and continues fairly steadily during the period in which the actual level of estrogen is rising.

Arteries and tendons tend to calcify with aging, the brain and pineal gland, kidneys and other organs retain more calcium and gradually lose functions, and cells die with a calcium overload.

Estrogen's stimulation of iron absorption was ignored by people who wanted to sell iron pills (often 18 mg per day) to women who lost iron (maybe 5 mg per month) by menstruation. After menopause, women absorb iron so fast that their body's iron load generally catches up with men's within a few years, at which time their incidence of heart attacks becomes similar to men's. If estrogen is a major factor in the promotion of iron absorption, **women's accelerated iron retention after menopause argues for the existence of a *more estrogenic state than when they were younger.*** Since progesterone falls sharply at menopause, the effect of the unopposed estrogen is going to be very strong, even as the absolute quantities of estrogen are declining.

When progesterone falls, the effects of cortisol, as well as estrogen, are increased, because progesterone antagonizes both of those hormones. Under the influence of cortisol, fat cells produce estrogen, and this effect is normally inhibited by progesterone and thyroid.

Calcification of soft tissues and iron retention accelerate at menopause. The body accumulates calcium, but it isn't going into the bones. The body accumulates iron, and it too goes into the soft tissues. Increased iron storage in the liver is associated with insulin resistance, and increased iron in any tissue is associated with increased lipid peroxidation in stress.

Calcium and iron tend to be deposited together, and the mitochondria are usually the starting points for their deposition. Iron overload has been implicated in heart disease, cancer, diabetes, and many other degenerative diseases, including the brain diseases.

Estrogen, and the free fatty acids that are liberated under its influence, increase the permeability of blood vessels, allowing water, proteins, etc., to leak out into the tissues. Tumor necrosis factor, induced by estrogen, reduces the "blood

brain barrier" function, promoting brain inflammation. The "blood brain barrier" means that water soluble molecules are excluded, while oil soluble molecules enter freely. Highly charged particles such as metal ions are normally efficiently excluded from the brain, in proportion to their water-solubility..

The free unsaturated fatty acids associated with estrogen's influence cause brain edema and mitochondrial damage (Catisti, et al., 1999). Although the fatty acids enter cells and mitochondria easily because the cytoplasm and mitochondria are lipophilic, unsaturation of a fat makes it a little less fat soluble, and more water soluble. Unsaturation also makes the fat more likely to be oxidized into toxic products, and to damage the mitochondria, suppressing its respiration, and forcing the cell into the less efficient glycolytic metabolism, raising the cell's pH, which makes the cell take up more water.

All of the biochemical features of Alzheimer's disease are consistent with prolonged estrogen excess. Estrogen's toxicity to the developing brain was established in the 1950s and 1960s. Maybe it's a kind of progress, that the claimed benefits of estrogen have aged with the drug industry: in 1940 estrogen helped you get pregnant, in 1950 it helped you to maintain pregnancy, in 1960 it helped to prevent or interrupt pregnancy, in 1970 it helped you retain calcium and iron to build strong bones and blood, in 1960 and 1990 it helped prevent heart attacks, and now finally it has nothing left to do but to prevent senile dementia.

The virologist, Gajdusek, wanted to argue that his virus, and not the accumulation of aluminum, was responsible for kuru and other brain degenerative diseases, and so he did a survey of brains of demented people from regions with different types of soil, and showed that the most abundant metals in the environment showed up in the brains. He argued that this showed that the metal deposition was just the consequence of a viral disease, rather than the cause of the brain degeneration. He observed that the deposits consisted mainly of calcium in regions that didn't have large amounts of other metals, so he argued that a particular metal such as aluminum couldn't be responsible for brain degeneration. But he didn't consider that factors other than viruses might be responsible for the brain mineralization that he saw.

Although women have more osteoporosis and more Alzheimer's disease than men do, the *lack* of estrogen is currently blamed for both of the problems. Why would Alzheimer's disease be so different from the other predominantly female diseases that have been linked to excess estrogen? Why would women's brains be different from men's? Why would their nerve cells degenerate without estrogen, while men's don't? Obviously women's brains and nerves aren't very different from men's and there simply isn't any sensible reason to believe that "estrogen deficiency" is responsible for Alzheimer's disease, or for osteoporosis, or for heart disease, or any of the other problems that have been blamed on the "menopausal estrogen deficiency."

The mass media find and publicize the things they want to believe, or want the public to believe. "Coffee causes heart disease," "estrogen prevents Alzheimer's disease," they say. How do they make the argument? Using plausible sounding terms that hide the real situation is the general technique. I don't want to give science reporters disproportionate blame, because specious argumentation is habitually practiced by many of the professors and researchers who provide the raw material for the news reports. In literature, "poetic diction" is intended to put the reader into a certain frame of mind, to be receptive to the poet's purpose. Many scientists rely on something like "poetic diction."

For example, a San Francisco study by Kristine Yaffe and co-authors found that "free estrogen," "the active form of the hormone," was higher in more of the people who had better cognitive function. Yaffe, et al., also found that dementia is associated with both depression and osteoporosis.

There isn't really such a thing as "free estrogen," which is defined in terms of a particular laboratory situation that doesn't correspond to anything in the body. Estrogen is insoluble in water, unless there is a large amount of alcohol present as solvent. When solids are present in a solution, estrogen passes directly from one solid to another, according to the momentary properties

of the solids. The laboratory measurement of "free estrogen" is describing both a physiological and a physical fantasy.

"Protein bound estrogen" is an active form of estrogen, and the estrogen bound to albumin probably accounts for most of estrogen's activity. Free fatty acids, which compete with estrogen for binding to the steroid-binding globulin, probably modify the properties of the more abundant albumin so that it binds more estrogen in its active form, causing estrogen to move from other proteins, lipoproteins, and red blood cells onto the activated albumin. **The presence of fats bound to the albumin makes the albumin more lipophilic, fat-loving, and molecules are taken up into cells--especially brain cells--according to their solubility in fats. For fatty molecules, there is no "blood brain barrier."** The fact that albumin has variable lipophilicity makes it an effective mechanism for the transport and delivery of oil soluble molecules.

Yaffe, et al., in associating depression and osteoporosis with dementia, are arguing that estrogen deficiency is the cause of all three conditions. They offer some hypothetical mechanisms for how estrogen might prevent Alzheimer's disease. Observing that brain cells die in people with Alzheimer's disease, they mention that estrogen stimulates "dendritic sprouting" in brain cells, as if that could compensate for the loss of cells (it doesn't). They observe that estrogen delivers more tryptophan to the brain, increasing the production of serotonin, and that it inhibits the monoamine oxidases and other enzymes that inactivate transmitter substances, increasing the activity of adrenaline, serotonin, and other transmitter substances. They suggest that increased circulation caused by estrogen might protect the brain. Here, Yaffe, et al., have invoked **the serotonin myth and other myths, including the nitric oxide myth, to substantiate the estrogen myth.**

Serotonin doesn't "cure depression," and both serotonin and nitric oxide impair circulation and are toxic to brain cells. Both of them poison mitochondrial respiration. Estrogen increases the viscosity of blood, and impairs circulation and oxygenation in many other ways.

The actual level of estrogen rises all through the reproductive years, and at menopause, the reduction in antiestrogenic factors, such as progesterone, thyroid, and DHEA, leads to increased effects of estrogen. The increased burden of unsaturated fatty acids that accumulate with aging clearly promotes the effects of estrogen and interferes with the production of the antiestrogenic hormones. These unsaturated fats cause progressive slowing of the metabolic rate, with particularly sharp decreases around puberty and menopause. As they interfere with the production of energy, they tend to increase cellular energy requirements, by promoting excitatory cellular processes.

Estrogen and PUFA create insulin resistance, and the resulting state of "diabetes" and stress de-energizes tissues, with the mitochondria that are damaged by unsaturated fatty acids, nitric oxide, tumor necrosis factor (TNT), serotonin, etc., failing to meet the tissues' energy needs. Stress, endotoxinemia, and increased estrogen tend to activate TNF, which has a role in brain degenerative diseases and osteoporosis and multiple organ failure. Much research has focussed on a search for a single substance that is responsible for the inflammatory conditions of Alzheimer's disease, but inflammation and aging are processes that involve many causes and mediators, with each individual's history causing variations in the details.

"Diabetes," or the inability to oxidize glucose vigorously, is simply a description of the metabolic aspect of cellular degeneration. The neurological impairment that is so commonly associated with officially diagnosed diabetes is simply one aspect of a general cellular malfunction that follows from chronic energy deprivation. Exactly the same processes occur in the sudden organ failure produced by shock, or the gradual organ failures--lungs, liver, kidney, heart, thymus, brain--that occur in aging. In general, there is a failure of circulation that exacerbates the metabolic and functional failures.

Diabetes, of both the insulin dependent and the non-insulin dependent types, is commonly associated with increased cortisol. In diabetes, inflammatory conditions, and under the influence

of increased cortisol, brain cells are deprived of glucose.

Increased cortisol is a normal response to the cell-damaging effects of stress or inflammation, but cortisol itself causes the death of nerve cells and immune cells through excitotoxicity, by blocking glucose metabolism. Estrogen increases cortisol production in a variety of ways, acting both through the pituitary and directly on the adrenal glands. Estrogen promotes excitotoxic processes, by opposing progesterone and thyroid, by directly exciting nerve cells, and by increasing the activity of excitatory nerve transmitters. It also increases serotonin, which blocks energy production by its effect on mitochondria, as well as by impairing circulation..

At puberty, there is a sudden increase in the incidence of depression, especially in girls. Increased adrenaline, like increased cortisol, is a feature of depression, stress, and inflammation; mobilizing fats, it can become part of a vicious circle, in which free fatty acids cause insulin resistance, activating the stress reactions. Increased serotonin is a feature of inflammation, shock, stress, and depression, and, like histamine, is tied very closely to estrogen's effects.

Estrogen does have some of the effects mention by Yaffe, et al., but these effects should make a person wonder whether estrogen isn't an important factor in the development of Alzheimer's disease, rather than being its main preventive agent.

In Alzheimer's disease, there is a distinct decrease in blood pressure, and orthostatic hypotension is a common feature of dementia. Estrogen's relaxing effect on the blood vessels has been shown to allow blood pooling in the veins, producing orthostatic hypotension. Estrogen, acting directly and through mediators such as serotonin, decreases the heart's pumping efficiency.

Blood viscosity is increased in Alzheimer's disease, and estrogen is known to increase blood viscosity.

Nitric oxide, a third cultic substance along with serotonin and estrogen, is invoked as a normalizer of brain circulation and protector of nerve cells from peroxidation. Whether a substance is an antioxidant or pro-oxidant depends on its environment, and both nitric oxide and estrogen are pro-oxidants, promoters of lipid peroxidation and other forms of cell damage, under a variety of physiological situations.

If authors are criticizing a well known doctrine, it is reasonable for them to assume that their readers know the arguments in favor of that doctrine, and to concentrate on their critical points. But Yaffe, et al., are arguing *in favor* of a well known doctrine. They fail to present the actual research situation. For them to ignore the work of people like Brawer, Desjardins, Schipper, and Liehr, who have explored the cytotoxic and neurotoxic effects of estrogen, amounts to simple propaganda. When such material is published in the mass media, such as JAMA, its effect can be considered as equivalent to fraud, since these media don't publicize alternative views.

While there has been some publicity about a recent study that found that treating Alzheimer's patients with estrogen for 12 weeks didn't improve their mood or mental ability, there has been relative silence about all the studies that show actual deterioration of mentality or mood in association with increased estrogen.

In old men, higher estrogen was found to be associated with lower mental ability (Barret-Connor, et al., 1999). Although estradiol is the most potent estrogen, estrone is the main estrogen in the circulation in terms of its quantity, and women's mental performance was found to be lower when the estrone was higher (Yaffe, et al., 1998).

Antiendorphin, antiexcitotoxic, anticholinergic, antiserotonergic, antiprostaglandin, and antiglucocorticoid drugs have been used with good effect in various degenerative nervous diseases, but all the so-called "anti" drugs are imprecise antagonists, and have many side effects. The natural antagonists and nutrients are usually helpful. Protein, sodium, magnesium, carbon dioxide/bicarbonate, progesterone, thyroid, vitamins, etc., can be curative in many brain diseases, but are seldom tried because of cultic medical ideas about nutrition, hormone tests, and the nature of cells and disease.

To the extent that unsaturated fats, heavy metals, and estrogenic substances (such as soybean products; tofu, for example, was recently implicated in dementia) can be avoided, the interactive processes of cell damage can be retarded. Natural restorative processes can maintain tissue integrity if the destructive processes are slowed.

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J Clin Endocrinol Metab 1999 Oct;84(10):3681-5. **Endogenous sex hormones and cognitive function in older men.** Barrett-Connor E, Goodman-Gruen D, Patay B. ."In age- and education-adjusted analyses, **men with higher levels of total and bioavailable estradiol had poorer scores on the BIMC Test and Mini-Mental State Examination**. Men with higher levels of bioavailable testosterone had better scores on the BIMC Test and the Selective Reminding Test (long-term storage)." "All associations were relatively weak but independent of age, education, body mass index, alcohol use, cigarette smoking and depression. **In these older men, low estradiol and high testosterone levels predicted better performance on several tests of cognitive function.** Linear and nonlinear associations were also found, suggesting that an optimal level of sex hormones may exist for some cognitive functions."

J Am Geriatr Soc 1998 Jul;46(7):816-21. **Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women.** Yaffe K, Grady D, Pressman A, Cummings S. **"Women in the higher estrone quartiles had 15% lower (worse) scores on Digit Symbol** compared with the lower quartiles (P=.004) but there was no difference by quartile on the modified MMSE or on Trails B. Cognitive function test scores declined over the 5 years of follow-up. There was no difference in amount of change by quartile of estradiol, **but women in the higher estrone quartiles had greater reduction of scores on Trails B compared with those in the lower quartiles (P=.012), even after adjusting for age, education, depression, stroke history, weight, and change in weight** since age 50. The age-adjusted odds of cognitive decline (defined as tenth percentile of women with the largest decline in cognitive performance) did not vary across quartile of estrone or estradiol. CONCLUSIONS: Endogenous estrogens are not associated consistently with cognitive performance or risk of cognitive decline on a selected battery of cognitive tests in older community-dwelling women. **Worse performance on two cognitive tests among women with higher estrone levels was surprising and warrants further investigation."**

FEBS Lett 1999 Dec 24;464(1-2):97-101. **The participation of pyridine nucleotides redox state and reactive oxygen in the fatty acid-induced permeability transition in rat liver mitochondria.** Catisti R, Vercesi AE. "Here, we have compared the PTP opening ability of arachidonic acid (AA) with that of carbonyl cyanide-p- rifluoromethoxyphenylhydrazone (FCCP) at concentrations that cause similar quantitative dissipation of the membrane potential (DeltaPsi) in Ca(2+)-loaded rat liver mitochondria respiring on succinate." "This second phase of DeltaPsi dissipation could also be prevented by rotenone or NAD(P)H-linked substrates which decrease the pyridine nucleotide (PN) oxidation that follows the stimulation of oxygen consumption induced by AA or FCCP. These results suggest that, under the experimental conditions used here, the PTP opening induced by AA or FCCP was a consequence of PN oxidation. Exogenous catalase also inhibited both AA- and FCCP-induced PTP opening. These results indicate that a condition of oxidative stress associated with the oxidized state of PN underlies membrane protein thiol oxidation and PTP opening."

FEBS Lett 2000 Jul 28;478(1-2):29-33. **The redox state of endogenous pyridine nucleotides can determine both the degree of mitochondrial oxidative stress and the solute selectivity of the permeability transition pore.** Zago EB, Castilho RF, Vercesi AE. "We propose that the shift from a low to a high conductance state of the PTP can be promoted

by the oxidation of NADPH. This impairs the antioxidant function of the glutathione reductase/peroxidase system, strongly strengthening the state of mitochondrial oxidative stress."

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Annu Rev Nutr 1997;17:37-50. **Toxic and essential metal interactions.** Goyer RA. Cadmium, lead, mercury, and aluminum are toxic metals that may interact metabolically with nutritionally essential metals. Iron deficiency increases absorption of cadmium, lead, and aluminum. Lead interacts with calcium in the nervous system to impair cognitive development. Cadmium and aluminum interact with calcium in the skeletal system to produce osteodystrophies. Lead replaces zinc on heme enzymes and cadmium replaces zinc on metallothionein. Selenium protects from mercury and methylmercury toxicity. Aluminum interacts with calcium in bone and kidneys, resulting in aluminum osteodystrophy. **Calcium deficiency along with low dietary magnesium may contribute to aluminum-induced degenerative nervous disease.**

Mech Ageing Dev 1998 May 1;102(1):1-13. **Iron accumulation in aging: modulation by dietary restriction.** Cook CI, Yu BP. "Male Fischer 344 rats fed ad libitum or dietary restricted (maintained on 60% of ad libitum food intake) were sacrificed at 6, 12 and 24 months of age." "Tissue total iron content was shown to increase significantly with age in animals fed ad libitum (AL). At 24 months, these animals showed comparable iron content increases in the liver and kidney, but were significantly greater than measurements found in brain. This age-related iron accumulation, however, was found to be markedly suppressed by dietary restriction (DR) in all tissues. Similarly, LPO measurements increased in an age-related, tissue-specific fashion. **At 24 months of age, measurements of LPO in AL rats brain and liver exceeded measurements in kidney. Again, we found DR to markedly suppress age-related LPO in all tissues.** Reported here are our findings on the ability of DR to modulate iron status at the tissue level. Consistent with the proposed anti-oxidative mechanism of DR, these findings further suggest that the modulation of tissue total iron content is an important component of that mechanism.

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Ray Peat's Newsletter

Not for republication without written permission. Raymond Peat, PO Box 5764, Eugene OR 97405 January 2001

Fibrosis is an outstanding feature of aging: Skin, joints, liver, kidneys, heart and blood vessels, even the brain, undergo fibrotic changes in association with disease, injury, and aging.

Excitotoxins are fibrogenic

Estrogen is excitotoxic and fibrogenic

Lactate is fibrogenic

Edema precedes fibrosis

Injury and inflammation are fibrogenic

Free radical peroxidation is a common pathway leading to fibrosis, as in cirrhosis of the liver in which unsaturated fats and free radicals have central roles.

Saturated fats, antihistamines, thyroid hormone, and other antiinflammatory agents prevent or reverse fibrosis.

The fibrous extracellular material regulates specialized cellular functioning, and is a protective buffer.

Fibrogenesis commonly precedes carcinogenesis.

Cancerization is a "field process," not primarily a unique "genetic event."

Proteolytic enzymes continuously dissolve and remodel the extracellular matrix.

Unsaturated fats inhibit proteolytic enzymes.

The resistance of the fibrin in blood clots to enzymic dissolution is increased by unsaturated fats.

Antifibromatogenic hormones oppose the development of the fibromas and cancers that are caused by estrogen.

The first principle in reversal is to stop the pathogenic process, and to stop the stress- induced cell death. Then restorative processes can come into balance with degenerative.

FIBROSIS: Estrogen, stiffness, excitotoxicity, aging--a problem more general than "collagen disease"

Thirty years ago, my professors said that any publication more than ten years old wasn't worth reading; that was apparently why I never saw the professors in the library. In a span of ten years, a change of 45 degrees in scientific orientation is thought to be progress. But in 40 years, those changes of orientation can produce a turn of 180 degrees, in which things that once seemed to be firmly established and full of potential have simply been removed from the academic canon. The biology of fibrosis is one of those important things that came to be neglected even while massive amounts of new evidence were confirming the old views.

At the beginning of the 20th century, Eli Metchnikov argued that changes in the connective tissues were the cause of aging. He also argued that intestinal toxins were important causes of the aging changes.

Early in the century, x-rays were found to produce tissue burns. The early effect of a radiation burn is inflammation and edema. The edema gradually gives way to fibrosis, and if the person lives long enough, the fibrotic tissue may calcify.

In the 1930s, Leo Loeb found that large doses of estrogen stimulated massive synthesis of collagen in the uterus.and vagina, and noticed that these effects resembled the increased accumulation of collagen that occurs with aging. In the 1940s, Alexander Lipshutz showed that very small, but continuous, doses of estrogen caused fibromas to develop in many tissues besides the uterus, and that these fibromas tended to develop

into cancers. Later, estrogen was found to accelerate the stiffening of the collagenous tissues that normally occurs with aging.

In the 1930s, the Shutes, father and sons, found that the clotting-associated diseases of pregnancy were prevented by vitamin E, and they proposed that vitamin E acts as an antiestrogen, protecting against the increased clotting problems caused by excessive estrogen. They showed that vitamin E activates the proteolytic, fibrinolytic, enzymes that remove blood clots.

Conventional beliefs identified vitamin E as an antioxidant that prevented oxidation of unsaturated fats, and this function of vitamin E appeared to make it inconceivable that vitamin E could also be of value in relation to the circulatory system. This attitude was still dominant in the 1970s among dietitians, physicians, and university professors. Besides ignoring or ridiculing the Shutes' work, mainstream journals would occasionally publish papers denying that vitamin E facilitates clot removal, or that estrogen promotes clotting, attempting to defend their 180 degree turn.

Just after the turn of the century, unsaturated fats were found to inhibit proteolytic enzymes. Repeatedly, the presence of unsaturated fatty acids has been shown to impair clot removal, either by its effect on proteolytic enzymes, or by being incorporated into the clot and making it resistant to dissolution.

Fibrin, the material that forms blood clots, is always in the process of formation and dissolution, in a kind of equilibrium. A thin layer of it coats the outside of blood cells, and the inside of blood vessels. When capillaries are leaky, some of the fibrin and its depolymerized subunits, leak out into the tissues. There is a complex interaction between fibrin and collagen, in which fibrin stimulates the formation of collagen (AJ Gray, et al., 1995) and collagen stimulates the fibrin clotting process.* Fibrin clots stimulate the growth of fibroblasts, and leaky blood vessels (Brown, et al., 1989) can lead to tissue fibrosis, though there are routes to fibrosis that don't involve fibrin.

Blood vessels leak under the influence of estrogen, irradiation, oxygen deprivation, vitamin E deficiency, free fatty acids, lactic acid, and various stress mediators, such as histamine and serotonin; particles as large as red blood cells can pass right through the endothelial cells. The loss of the blood vessels' ability to serve as a barrier corresponds to a disturbance in the structure of the cells, and this structural permeability is apparently the result of an imbalance in the state of the electrons in the proteins, the redox (reduction and oxidation) state, regulated by glutathione and other antioxidants and energy regulators.

The internal state of any cell, not just in the blood vessels, is governed in similar ways by cellular energy and the redox state of proteins, and in the oxidatively disturbed state, cells take up water, as well as being abnormally "permeable" in both directions. For example, when a cell is deficient in vitamin E it loses molecules such as ATP and proteins, that diffuse out into the extracellular spaces. When cells are in an energy deficient state, as in hypothyroidism, they are in this leaky, edematous state.

This state of near exhaustion is similar to the "excitotoxic" state that's caused by an imbalance between stimulation and energy production. In the brain, excitotoxins have been found to produce a kind of fibrosis, in which the cells that normally produce the myelin sheath surrounding nerve axons begin producing collagen, and appear to change into a type of cell (Schwann cell) that is not normally found in the brain. **The production of collagen seems to be a very basic kind of defensive reaction to excessive stimulation or oxygen deprivation.** This makes it possible to see "excitotoxicity" as a general process, that includes the kind of fibrosis and calcification of skin that Hans Selye produced (by combining vitamin E deficiency with heavy metal toxicity and local

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**In the 1920s, W. F. Koch was proposing that oxidative free-radical processes governed the clotting of blood, the healing of wounds, and possibly the calcification of devitalized tissues. At that time, free radicals were an esoteric matter of interest mainly to a few polymer chemists, and it was considered absurd to suggest that cellular respiration could relate to extracellular fibrous matter.*

irritation), as well as the aging of brain cells produced by prolonged estrogenic stimulation. Scleroderma, like the other "collagen diseaes," affects women (during their reproductive years) much more often than men. Retroperitoneal fibrosis, which can seriously damage the kidneys and other abdominal organs, has been compared to uterine fibroid tumors, and it is commonly treated successfully with the antiestrogenic drug, tamoxifen. Tamoxifen has also been used to treat keloids and to prevent abnormal scars in plastic surgery. (I have seen keloids regress quickly following the application of vitamin E with antiestrogenic hormones.) The fibrotic response to the excitotoxic imbalance can be seen in practically all chronic and degenerative diseases.

Fibrosis is an abnormal progression of the normal formation of fibrous material between cells, and it usually involves an increase in the volume of the extracellular material, and an increase in the percentage of collagen in that matrix, and an increased rigidity of the collagen that results from chemical cross-links, that are analogous to the polymerization of a plastic, or the vulcanizing of rubber. Arteriosclerosis is probably the best known medical example of tissue fibrosis, but it's the same phenomenon that makes the meat from an old animal tough and rubbery.

Although "stiffness" is a familiar term in engineering and biology, it has some different meanings in different situations. When a tissue swells up with water until it's tight, it is stiffer than in its natural condition. The material of tendons and ligaments gets stiffer by increasing its density and toughness. When a bone gets old, it gets brittle and weak, and in one sense it is stiffer than a child's bone, since a child's bone can be deformed without breaking. While the engineering definitions can't be applied to all tissues in a simple way, biologically it's useful to think of stiffness as something that progresses along with fibrosis, as the function of a tissue decreases. In the first stage of tissue injury, swelling stiffens a tissue; after prolonged edema, there may be an increased volume and concentration of collagen around cells; finally, the density of the collagen can increase, and can calcifiy, as in the sclera of the eye, the arteries, heart valves, pericardium, and even the heart muscle itself.

In diseases of stress and aging, there is a general inflammatory state, that can end in multiple organ failure. Congestive heart failure illustrates some of the effects of this energy-poor, inflamed and edematous state: The heart's function is reduced because of stiffness caused by increased water and calcium in the cells; at the same time, arteries are stiff and resistant, impairing the flow of blood and making regulation of blood pressure difficult. In chronic hypothyroidism, the heart gradually becomes fibrotic, and this provides an opportunity for calcification to occur.

If a callus is a metaphor for the normal, protective function of connective tissue, then a corn is a metaphor for the harmful overdevelopment of the protective reaction. The ordinary minor mechanical tensions and pressures that occur in any living animal, as well as the biochemical gradients produced by metabolizing cells, shape the connective tissues that keep cells in their particular place in the organism. When gelatin, made by boiling connective tissues in water, is injected into a growing organism, the randomly arranged molecules of the melted collagen can be seen to organize themselves back into the coherently aligned cable-like structures of normal connective tissue.

Cells decide what they will be and do according to their surroundings. Normally, cells live in contact with a layer of non-cellular material containing fibrous and elastic and gelatinous material, that functions as a medium of communication with other cells. Irritation, stress, and shock commonly produce a series of tissue reactions, including edema, fibrosis, calcification, and death, but with certain possible alternatives, such as a return to the normal state, or early cell death, or lipodystrophy (fatty degeneration), or tumefaction (development into a tumor).

Although there are specialized cells, fibroblasts, that form large amounts of connective tissue, they are very closely related to muscle cells, fat cells, and glial cells, and the functions of one can sometimes change into those of another type. One of the main problems of biology in the

last century has been to understand the factors that cause one kind of cell to change into another. One of the functions of the collagen layer secreted around cells appears to be to provide a degree of insulation from the numerous "inductive" factors, so that a cell can remain what it is.

Conditions in the whole organism affect the way an individual cell will relate to its immediate environment. Nutritional deficiencies or imbalances will make special demands on certain types of tissue. Increased collagen production can provide some protection against toxins, but the protective layer also limits the cells' access to the blood supply.

Cells in their excited and exhausted state are increasingly open to penetration of the toxins, because of their own increased permeability, and because of the increased leakiness of the blood vessels. Certain environmental toxins accumulate more rapidly as the cells lose their ability to destroy them. Several kinds of toxin, including the unsaturated fats, inhibit the proteolytic enzymes that remodel tissue, and reduce the ability to dismantle and rebuild the extracellular matrix.

Collagen is a very unusual protein, since it lacks tryptophan and cysteine, and contains a very high percentage of glycine. Glycine is the simplest amino acid, and serves as an inhibitory transmitter. It has some remarkable protective activities against toxins, but even the process of forming it has some uniquely protective consequences: It is made from sugar, with the addition of ammonia removed from glutamic acid, leaving ketoglutaric acid as the product; ketoglutarate is a component of the Krebs cycle. In effect, the formation of glycine helps to eliminate an excitotoxin while replenishing the pathway of oxidative metabolism. When collagen is dissolved, a large amount of the antitoxic glycine is released, but not a bit of the excitotoxic antithyroid amino acids cysteine and tryptophan.

The increased energy deficiency produced by accumulated toxins and fibrosis can stimulate the production of porphyrins for the heme enzymes that control respiration and detoxification, and this can lead to the production of carbon monoxide and other anti-respiratory factors. Increasing amounts of ammonia and lactic acid circulate through the tissues. As excitatory states replace the capacity for resting inhibition, increased amounts of many hormones and other signal substances circulate, and many of them are produced in unusual sites, often in the same tissues that respond to them, as when a breast cancer produces estrogen. In the absence of communication between the tissue and its environment, these locally produced factors probably serve to maintain local homeostasis, but at the expense of the functions of the whole organism.

In every different part of the body, the extracellular matrix reflects the individuality of its cell types and their particular function. But as the body's exposure to toxic imbalances progresses, the general properties of deterioration start to become more important than the specialized functions.

To reverse this process, it's necessary to avoid doing the things that caused the problem to develop. The accumulation of heavy metals and of the unstable unsaturated fats (linoleic, linolenic, and arachidonic acids) can be slowed or reversed by careful dietary choices. The calorie-restricted diets that slow the aging process reduce the accumulation of the unstable fats and the heavy metals. Vitamin E reduces the vascular leakiness and the free radical peroxidation that are so closely involved in fibrosis. Since serotonin and nitric oxide are involved in these processes, they should be minimized by keeping carbon dioxide production high (by optimizing thyroid function), and by eating proteins that have a safe balance of the amino acids. Too much arginine increases nitric oxide formation, and too much tryptophan increases serotonin production. Too much glutamic acid aspartic acid, and cysteine can be directly excitotoxic, and the metabolites of cysteine include proinflammatory homocysteine, which can disrupt collagen structure.

Since estrogen is often a promoter of fibrosis, acting in a variety of ways, it should be kept under control by eating enough protein, keeping thyroid function relatively high, and if necessary by using progesterone and other antiestrogenic hormones. A protein deficiency is thrombogenic (clot forming), and probably excitotoxic.

Magnesium, taurine, and niacinamide have many protective functions, and can help to reduce or reverse inflammatory and fibrogenic processes.

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Ray Peat's Newsletter

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Mary Shomon interview

Mary Shomon: Why do women with treated hypothyroidism frequently still have inappropriately high levels of cholesterol and high triglycerides, and what can they do to help lower these levels?

RP: Often it's because they were given thyroxine, instead of the active thyroid hormone, but hypertriglyceridemia can be caused by a variety of things that interact with hypothyroidism. Estrogen treatment is a common cause of high triglycerides, and deficiencies of magnesium, copper, and protein can contribute to that abnormality. Toxins, including some drugs and herbs, can irritate or stimulate the liver to produce too much triglyceride. T3, triiodothyronine, is the active thyroid hormone, and it is produced (mainly in the liver) from thyroxine, and the female liver is less efficient than the male liver in producing it, as is the female thyroid gland. The thyroid gland, which normally produces some T3, will decrease its production in the presence of increased thyroxine. Therefore, thyroxine often acts as a "thyroid anti-hormone," especially in women. When thyroxine was tested in healthy young male medical students, it seemed to function "just like the thyroid hormone," but in people who are seriously hypothyroid, it can suppress their oxidative metabolism even more. It's a very common, but very serious, mistake to call thyroxine "the thyroid hormone."

Nov. 6, 2000, email interview with Mary Shomon for her website:
www.thyroid.about.com/library/weekly/aa110800c.htm
References weren't included in the interview.

High cholesterol is more closely connected to hypothyroidism than hypertriglyceridemia is. Increased T3 will immediately increase the conversion of cholesterol to progesterone and bile acids. When people have abnormally low cholesterol, I think it's important to increase their cholesterol before taking thyroid, since their steroid-forming tissues won't be able to respond properly to thyroid without adequate cholesterol.

MS: You feel that progesterone can have anti-stress effects, without harming the adrenal glands. Is progesterone therapy something you feel is useful to many or most hypothyroid patients? How can a patient know if she needs progesterone? Do you recommend blood tests? And if so, at what point in a woman's cycle?

RP: Estrogen blocks the release of hormone from the thyroid gland, and progesterone facilitates the release. Estrogen excess or progesterone deficiency tends to cause enlargement of the thyroid gland, in association with a hypothyroid state. Estrogen can activate the adrenals to produce cortisol, leading to various harmful effects, including brain aging and bone loss. Progesterone stimulates the adrenals and the ovaries to produce more progesterone, but since progesterone protects against the catabolic effects of cortisol, its effects are the opposite of estrogen's. Progesterone has antiinflammatory and protective effects, similar to cortisol, but it doesn't have the harmful effects. In hypothyroidism, there is a tendency to have too much estrogen and cortisol, and too little progesterone.

The blood tests can be useful to demonstrate to physicians what the problem is, but I don't think they are necessary. There is evidence that having 50 or 100 times as much progesterone as estrogen is desirable, but I don't advocate

"progesterone replacement therapy" in the way it's often understood. Progesterone can instantly activate the thyroid and the ovaries, so it shouldn't be necessary to keep using it month after month. If progesterone is used consistently, it can postpone menopause for many years.

Cholesterol is converted to pregnenolone and progesterone by the ovaries, the adrenals, and the brain, if there is enough thyroid hormone and vitamin A, and if there are no interfering factors, such as too much carotene or unsaturated fatty acids.

Progesterone deficiency is an indicator that something is wrong, and using a supplement of progesterone without investigating the nature of the problem isn't a good approach. The normal time to use a progesterone supplement is during the "latter half" of the cycle, the two weeks from ovulation until menstruation. If it is being used to treat epilepsy, cancer, emphysema, multiple sclerosis, migraine or arthritis, or something else so serious that menstrual regularity isn't a concern, then it can be used at any time.

MS:: What supplements do you feel are essential for most people with hypothyroidism?

RP: Because the quality of commercial nutritional supplements is dangerously low, the only supplement I generally advocate is vitamin E, and that should be used sparingly. Occasionally, I will suggest limited use of other supplements, but it is far safer in general to use real foods, and to exclude foods which are poor in nutrients. Magnesium is typically deficient in hypothyroidism, and the safest way to get it is by using orange juice and meats, and by using epsom salts baths; magnesium carbonate can be helpful, if the person doesn't experience side effects such as headaches or hemorrhoids.

MS: Do you feel that there are any special considerations, issues, or treatments for men with hypothyroidism?

RP: Thyroid supplements can be useful for prostate hypertrophy and some cases of impotence and infertility. Occasionally, a man who can't put on a normal amount of weight finds that a thyroid supplement allows normal weight gain. Leg cramps, insomnia and depression are often the result of hypothyroidism. Heart failure, gynecomastia, liver disease, baldness and dozens of other problems can result from hypothyroidism.

MS: Many people describe how they are clinically hypothyroid, with elevated TSH levels, but have extremely high pulse rates. Do you have any thoughts as to what might be going on in that situation?

RP: In hypothyroidism, thyrotropin-release hormone (TRH) is usually increased, increasing release of TSH. TRH itself can cause tachycardia, "palpitations," high blood pressure, stasis of the intestine, increase of pressure in the eye, and hyperventilation with alkalosis. It can increase the release of norepinephrine, but in itself it acts very much like adrenalin. TRH stimulates prolactin release, and this can interfere with progesterone synthesis, which in itself affects heart function.

I consider even the lowest TSH within the "normal range" to be consistent with hypothyroidism; in good health, very little TSH is needed. When the thyroid function is low, the body often compensates by over-producing adrenalin. The daily production of adrenalin is sometimes 30 or 40 times higher than normal in hypothyroidism. The adrenalin tends to sustain blood sugar in spite of the metabolic inefficiency of hypothyroidism, and it can help to maintain core body temperature by causing vasoconstriction in the skin, but it also disturbs the sleep and accelerates the heart. During the night, cycles of rising adrenalin can cause nightmares, wakefulness, worry, and a pounding heart. Occasionally, a person who has chronically had a heart rate of 150 beats per minute or higher, will have a much lower heart rate after using a thyroid supplement for a few days. If your temperature or heart rate is lower after breakfast than before, it's likely that they were raised as a result of the nocturnal increase of adrenalin and cortisol caused by hypothyroidism.

M.S.: You have written that for some people, there is a problem converting T4 to T3, but that

diet can help. You recommend a piece of fruit or juice or milk between meals, plus adequate protein, can help the liver produce the hormone. Can you explain a bit more about this idea and how it works?

R.P.: The amount of glucose in liver cells regulates the enzyme that converts T4 to T3. This means that hypoglycemia or diabetes (in which glucose doesn't enter cells efficiently) will cause hypothyroidism, when T4 can't be converted into T3. When a person is fasting, at first the liver's glycogen stores will provide glucose to maintain T3 production. When the glycogen is depleted, the body resorts to the dissolution of tissue to provide energy. The mobilized fatty acids interfere with the use of glucose, and certain amino acids suppress the thyroid gland. Eating carbohydrate (especially fruits) can allow the liver to resume its production of T3.

M.S.: You have recommended if supplemental T3 is used, a thyroid patients "nibble on a 10-15 mg Cytomel tablet throughout the day." Can you explain why? Would compounded time-released T3 as available in some compounding pharmacies do the same?

R.P.: Most hypothyroid people can successfully use a supplement that contains four parts of thyroxine for each part of T3, but some people need a larger proportion of T3 for best functioning. The body normally produces several micrograms of T3 every hour, but if a large amount of supplementary thyroid is taken in a short time, the liver quickly inactivates some of the excess T3. Taking a few micrograms per hour provides what the body can use, and doesn't suppress either the liver's or the thyroid's production of the hormone. I have only rarely talked to anyone who had good results with the so-called time-release T3, and I have seen analyses of some samples in which there was little or no T3 present. It is hard to compound T3 properly, and the conditions of each person's digestive system can determine whether the T3 is released all at once, or not at all. I don't think there is a valid scientific basis for calling anything "time-release T3."

I have been told that the company which now owns the Armour name and manufactures "Armour thyroid USP" has added a polymer to the formula, and I think this would account for the stories I have heard about its apparent inactivity. Some people have found that the tablets passed through their intestine undigested, so I think it's advisable to crush or powder the tablets.

M.S.: You feel that excessive aerobic exercise can be a cause of hypothyroidism. Can you explain this further? How much is too much?

R.P.: I'm not sure who introduced the term "aerobic" to describe the state of anaerobic metabolism that develops during stressful exercise, but it has had many harmful repercussions. In experiments, T3 production is stopped very quickly by even "sub-aerobic" exercise, probably because of the combination of a decrease of blood glucose and an increase in free fatty acids. In a healthy person, rest will tend to restore the normal level of T3, but there is evidence that even very good athletes remain in a hypothyroid state even at rest. A chronic increase of lactic acid and cortisol indicates that something is wrong. The "slender muscles" of endurance runners are signs of a catabolic state, that has been demonstrated even in the heart muscle. A slow heart beat very strongly suggests hypothyroidism. Hypothyroid people, who are likely to produce lactic acid even at rest, are especially susceptible to the harmful effects of "aerobic" exercise. The good effect some people feel from exercise is probably the result of raising the body temperature; a warm bath will do the same for people with low body temperature.

M.S.: You feel that chronic protein deficiency is a common cause of hypothyroidism. How much protein should people get (as much as 70-100 grams a day?) and what types of protein, in order to prevent hypothyroidism?

R.P.: The World Health Organization standard was revised upward by researchers at MIT, and recently the MIT standard has been revised upward again by military researchers; this

is described in a publication of the National Academy of Sciences (National Academy Press, *The Role of Protein and Amino Acids in Sustaining and Enhancing Performance,* 1999). When too little protein, or the wrong kind of protein, is eaten, there is a stress reaction, with thyroid suppression. Many of the people who don't respond to a thyroid supplement are simply not eating enough good protein. I have talked to many supposedly well educated people who are getting only 15 or 20 grams of protein per day. To survive on that amount, their metabolic rate becomes extremely low. The quality of most vegetable protein (especially beans and nuts) is so low that it hardly functions as protein.

Muscle meats (including the muscles of poultry and fish) contain large amounts of the amino acids that suppress the thyroid, and shouldn't be the only source of protein.

M.S.: You talk about darkness and shorter days of winter as a stress. It's known that more thyroid hormone is needed by some patients during colder weather. Are there other things you recommend patients do to "winterproof" their metabolism?

R.P.: Very bright incandescent lights are helpful, because light acts on, and restores, the same mitochondrial enzymes that are governed by the thyroid hormone. In squirrels, hibernation is brought on by the accumulation of unsaturated fats in the tissues, suppressing respiration and stimulating increased serotonin production. In humans, winter sickness is intensified by those same antithyroid substances, so it's important to limit consumption of unsaturated fats and tryptophan (which is the source of serotonin). When a person is using a thyroid supplement, it's common to need four times as much in December as in July.

M.S.: You have reported that pregnenolone can be helpful for Graves' patients with exophthalmus. Can you explain further?

R.P.: Graves' disease and exophthalmos can occur with hypothyroidism or euthyroidism, as well as with hyperthyroidism. Pregnenolone regulates brain chemistry in a way that prevents excessive production of ACTH and cortisol, and it helps to stabilize mitochondrial metabolism. It apparently acts directly on a variety of tissues to reduce their retention of water. In the last several years, all of the people I have seen who had been diagnosed as "hyperthyroid" have actually been hypothyroid, and benefitted from increasing their thyroid function; some of these people had also been told that they had Graves' disease.

M.S.: You are a proponent of coconut oil for thyroid patients. Can you explain why?

R.P.: An important function of coconut oil is that it supports mitochondrial respiration, increasing energy production that has been blocked by the unsaturated fatty acids. Since the polyunsaturated fatty acids inhibit thyroid function at many levels, coconut oil can promote thyroid function simply by reducing those toxic effects. It allows normal mitochondrial oxidative metabolism, without producing the toxic lipid peroxidation that is promoted by unsaturated fats.

M.S.: Do you have any thoughts for thyroid patients who are trying to do everything right, and yet still can't lose any weight?

R.P.: Coconut oil added to the diet can increase the metabolic rate. Small frequent feedings, each combining some carbohydrate and some protein, such as fruit and cheese, often help to keep the metabolic rate higher. Eating raw carrots can prevent the absorption of estrogen from the intestine, allowing the liver to more effectively regulate metabolism. If a person doesn't lose excess weight on a moderately low calorie diet with adequate protein, it's clear that the metabolic rate is low. The number of calories burned is a good indicator of the metabolic rate. The amount of water lost by evaporation is another rough indicator: For each liter of water evaporated, about 1000 calories are burned.

M.S.: You have talked about internal malnutrition as a problem for many thyroid patients, due to insufficient digestive juices and poor intestinal

movements. Are there ways patients who are treated for hypothyroidism can help alleviate this problem.

R.P.: The absorption and retention of magnesium, sodium, and copper, and the synthesis of proteins, are usually poor in hypothyroidism.

Salt craving is common in hypothyroidism, and eating additional sodium tends to raise the body temperature, and by decreasing the production of aldosterone, it helps to minimize the loss of magnesium, which in turn allows cells to respond better to the thyroid hormone. This is probably why a low sodium diet increases adrenalin production, and why eating enough sodium lowers adrenalin and improves sleep. The lowered adrenalin is also likely to improve intestinal motility.

M.S.: You've mentioned eggs, milk and gelatin as good for the thyroid. Can you explain a bit more about this?

R.P.: Milk contains a small amount of thyroid and progesterone, but it also contains a good balance of amino acids. For adults, the amino acid balance of cheese might be even better, since the whey portion of milk contains more tryptophan than the curd, and tryptophan excess is significantly antagonistic to thyroid function. The muscle meats contain so much tryptophan and cysteine (which is both antithyroid and potentially excitotoxic) that a pure meat diet can cause hypothyroidism. In poor countries, people have generally eaten all parts of the animal, rather than just the muscles--feet, heads, skin, etc. About half of the protein in an animal is collagen (gelatin), and collagen is deficient in tryptophan and cysteine. This means that, in the whole animal, the amino acid balance is similar to the adult's requirements. Research in the amino acid requirements of adults has been very inadequate, since it has been largely directed toward finding methods to produce farm animals with a minimum of expense for feed. The meat industry isn't interested in finding a diet for keeping chickens, pigs, and cattle healthy into old age. As a result, adult rats have provided most of our direct information about the protein requirements of adults, and since rats keep growing for most of their life, their amino acid requirements are unlikely to be the same as ours.

M.S.: Do you think the majority of people with hypothyroidism get too much or too little iodine? Should people with hypothyroidism add more iodine, like kelp, seaweeds, etc.?

R.P.: 30 years ago, it was found that people in the US were getting about ten times more iodine than they needed. In the mountains of Mexico and in the Andes, and in a few other remote places, iodine deficiency still exists. Kelp and other sources of excess iodine can suppress the thyroid, so they definitely shouldn't be used to treat hypothyroidism.

M.S.: What are your thoughts for Graves' disease/hyperthyroidism patients? Should they move ahead quickly to get radioactive iodine treatment, or are there natural things they might be able to try to temporarily – or even permanently – get a remission?

RP: Occasionally, a person with a goiter will temporarily become hyperthyroid as the gland releases its colloid stores in a corrective process. Some people enjoy the period of moderate hyperthyroidism, but if they find it uncomfortable or inconvenient, they can usually control it just by eating plenty of liver, and maybe some cole slaw or raw cabbage juice. Propranolol will slow a rapid heart. The effects of a thyroid inhibitor, PTU, propylthiouracil, have been compared to those of thyroidectomy and radioactive iodine. The results of the chemical treatment are better for the patient, but not nearly so profitable for the physician.

Besides a few people who were experiencing the unloading of a goiter, and one man from the mountains of Mexico who became hypermetabolic when he moved to Japan (probably from the sudden increase of iodine in his diet, and maybe from a smaller amount of meat in his diet), all of the people I have seen in recent decades who were called "hyperthyroid" were not. None of the

people I have talked to after they had radioiodine treatment were properly studied to determine the nature of their condition. Radioiodine is a foolish medical toy, as far as I can see, and is never a proper treatment.

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Eur Heart J 1987 May;8 Suppl B:147-51 **Injection of thyrotropin releasing hormone into the locus coeruleus increases blood pressure.** Paakkari I, Siren AL, Nurminen ML, Svartstrom-Fraser M. Thyrotropin releasing hormone (TRH), 10 pmol kg-1 injected in the region of locus coeruleus, caused a rapid (within 1 min) rise of mean arterial pressure in **the urethane-anaesthetized rat. No clear-cut effects in heart rate or ventilation were observed. When TRH was injected into the lateral ventricle, a dose more than 10-fold higher was required to achieve a comparable rise in arterial pressure. It is concluded that TRH may have a physiological role in central cardiovascular regulation.**

Horm Metab Res 1987 Apr;19(4):164-7. **Cardiovascular, catecholamine and psychological responses to TRH in four types of affective disorder patients.** Kennedy B, Strassman RJ, Ziegler MG, Janowsky DS, Risch SC, Huey LY, Gillin JC When 500 micrograms of TRH is given intravenously, an increase in TSH, blood pressure, plasma catecholamines and positive emotions follows. Four groups of patients with major, minor or bipolar depression or schizoaffective disorder increased their TSH levels by similar amounts after TRH. The neurohormone also significantly increased diastolic blood pressure by 5.5 +/- 1.6 mm Hg, and decreased heart rate by 7.6 +/- 1.3 beats/min. There was a weak trend for bipolar depressives to have less cardiovascular response to TRH than the other **groups. Plasma norepinephrine (NE) was higher after TRH than after placebo. The NE response differed between patient groups (P = .0023) because of a smaller** response by major depressives. TRH decreased anger, tension and depression, and increased friendliness. Positive emotional responses were significantly greater in the bipolar depressives than in other groups. Forty-one other studies have found a subnormal TSH response does not distinguish between subtypes of the affective disorders, but cardiovascular, catecholamine and mood responses may do so.

Acta Physiol Scand 1983 Mar;117(3):427-37. **Effects of TRH and TRH analogues on the central regulation of breathing in the rat.** Hedner J, Hedner T, Wessberg P, Lundberg D, Jonason J Respiratory activity was studied in rats during light halothane anesthesia. Thyrotropin releasing hormone (TRH) and two TRH analogues: the desamidated form (TRH-OH) and gamma- butyrolactone- gamma-carbonyl-L-histidyl-L-prolinamide citrate (DN 1417) were administered intracerebroventricularly. TRH 0.5-5 micrograms induced a marked tachypnoea with a rapid onset and a duration of at least 20 min. DN 1417, a potent analogue of TRH with a very low TSH (thyroid stimulating hormone) releasing activity was more effective in stimulating respiratory frequency, while TRH-OH, regarded to have neither TSH releasing nor extra hypothalamic effects, at equimolar doses was unable to induce any changes in the respiratory pattern. When TRH was given into the fourth ventricle the dose response curve was slightly shifted to the left. In experiments employing the occluded breath technique, P0.1 was increased in the same magnitude as the mean inspiratory flow (VT/T1). The results also indicated an increase in the gain of the inflation reflex loop whereas the central bulbopontine setting for T1 and TTOT were not significantly changed. Local injection of TRH into the nucleus tractus solitarii induced a stimulation of respiratory frequency which was slower in onset compared to the response seen after injection into the lateral or fourth ventricles. Concomitantly to the respiratory changes, i.c.v. TRH **injection induced a hypocarbia and an alkalosis. No changes in blood pressure** or heart rate were seen. The respiratory stimulant effect of TRH could be potentiated by pretreatment with naloxone, methylatropine or a low dose of GABA. Haloperidol or propranolol did not significantly change the respiratory effects of TRH, while reserpine pretreatment seemed to blunt some of the ventilatory effects of TRH. It seems likely that TRH has few direct effects on brain stem neurones involved in the central regulation of respiration, but the main effects seem to be elicited in areas rostral to the brain stem. The respiratory stimulating effect of TRH is unrelated to TSH. Furthermore, other neurotransmitter systems might also be involved in modulation of the respiratory stimulation evoked by TRH.

Invest Ophthalmol Vis Sci 1989 Oct; 30(10): 2200-8. **Thyrotropin releasing hormone increases intraocular pressure. Mechanism of action.** Liu JH, Dacus AC, Bartels SP. Eye Research Institute of REtina Foundation, Harvard Medical School, Boston, Massachusetts. Intravenous injections of 1-100 micrograms thyrotropin releasing hormone (TRH) in rabbits elevated intraocular pressure (IOP). The 2-5 mm Hg increase of IOP lasted for less than 2 hr. No change of pupil size was observed. This IOP elevation was not due to a direct effect of TRH on ocular tissues since intravitreal injections of 0.1 and 1 micrograms TRH did not change IOP. Concentrations of thyroid stimulating hormone (TSH), triiodothyronine (T-3), epinephrine (Epi) and norepinephrine (NE) in the plasma were elevated at 30 min after an i.v. injection of 10 micrograms TRH. Plasma levels of prolactin and thyroxine were not changed. Bolus i.v.

injections of 0.1-1 micrograms TSH and 0.1-1 micrograms T-3, which would produce an equivalent increase of relevant hormones in the circulation, did not increase IOP. However, similar i.v. injections of 10-100 ng Epi and 100 ng NE caused a 1.5-3 mm Hg IOP elevation for 15-30 min. Thus, the IOP elevation following TRH administration probably is caused by the increase of circulating endogenous catecholamines and not by the stimulation of the TSH-thyroid hormone axis. Heart rate, but not blood pressure, was increased with 10 micrograms TRH. After unilateral transection of the cervical sympathetic trunk, the IOP elevation in the decentralized eye was larger than that in the intact eye. Topical treatment of 0.1% or 1% timolol in the decentralized eye inhibited the IOP elevations in both eyes, but 0.1% prazosin was not effective. **Topical 1% atropine and atropine given subcutaneously at 0.6 mg/kg decreased the bilateral IOP elevations. These observations indicate that beta-adrenergic and muscarinic mechanisms,** not an alpha-1-adrenergic mechanism, are involved.

Peptides 1990 Sep-Oct;11(5):939-44. **Selective cardiorespiratory activity of an iodinated analog of thyrotropin-releasing hormone (TRH).** Paakkari I, Jarvinen A, Vonhof S, Mannisto PT, Cohen LA, Labroo VM, Feuerstein G. The biological activity of thyrotropin-releasing hormone (TRH) and its analogs 4(5)-I-Im-TRH and 2,4(5)-I2-Im-TRH was assessed by means of their effects on: 1) the mean arterial pressure (MAP), 2) heart rate (HR), 3) ventilation minute volume (MV), 4) contractility of the rat duodenum, and 5) concentrations of thyrotropin (TSH) or prolactin (PRL) in serum. Also their binding to TRH-receptors in brain homogenates was studied. In urethane-anesthetized rats TRH ICV increased MAP, HR and MV. 4(5)-I-Im-TRH was equally as active as TRH on HR and MV but a significant elevation in MAP was observed only at a dose 100-fold to that of TRH. However, the maximal responses of 4(5)-I-Im-TRH and TRH did not differ. **In conscious rats, TRH 1A elevated MAP and HR** but 4(5)-I-Im-TRH was active on MAP only. 2,4(5)-I2-Im-TRH was devoid of cardiorespiratory activity. **TRH dose-dependently inhibited the contractions of the rat duodenum** while the iodinated analogs lacked such an activity. To induce a significant release of TSH several hundred times more of 4(5)-I-Im-TRH and over 1000 times more of 2,4(5)-I2-Im-TRH were needed as compared to TRH. The iodoanalogs elevated PRL levels only at doses 2000-fold higher than those of TRH. The iodoanalogs displaced [3H][3-Me-His2]TRH [(3H]MeTRH) from its binding sites at concentrations about 1000 times higher than those of TRH. Substitutions of the histidyl moiety of TRH in 4(5)-I-Im-TRH and 2,4(5)-I2-Im-TRH resulted in substantial loss of the endocrine activity. While the di-iodinated analog was **practically devoid of any biological activity the monoiodinated analog exerted similar cardiorespiratory activity to that of TRH.**

Arch Gen Psychiatry 1991 Feb;48(2):148-56. **Endocrine, cardiovascular, and behavioral effects of intravenous protirelin in patients with panic disorder.** Stein MB, Uhde TW Section on Anxiety and Affective Disorders, National Institute of Mental Health, Bethesda, Md 20892. The effects of protirelin administration on the anterior pituitary release of thyrotropin and prolactin were examined in 26 patients with panic disorder and 22 healthy volunteers. There were no differences observed in hormonal responses to protirelin between patients and controls. However, higher Beck Depression Inventory scores were associated with smaller baseline-corrected maximal changes in thyrotropin responses. Cardiovascular responses to protirelin did not differ between a subgroup of 15 patients with panic disorder and 15 age- and **sex-matched healthy controls. Although protirelin produced robust increases in heart rate and blood pressure, only one patient with panic disorder experienced** a panic attack during the infusion. The hormonal findings suggest that the presence of depressive symptoms may have a significant impact on various indexes of neuroendocrine responsivity and should be taken into consideration when looking at biologic measures in patients with panic disorder. The cardiovascular and behavioral findings do not support the hypothesis that all panic-producing stimuli are nonspecific and suggest that the induction of physical stimuli may be insufficient to produce panic attacks even in susceptible individuals.

Exp Clin Endocrinol 1992;99(3):143-6. **Time-related effects of thyrotropin-releasing hormone (TRH) on the pituitary-thyroid axis and extrathyroidal targets.** Nink M, Weber P, Krause U, Beyer J IIIrd. Thyrotropin-releasing hormone (TRH) is a tripeptide and acts as a stimulator of the pituitary-thyroid axis as well as having a great number of well defined extrathyroidal functions. Studies in experimental animals have shown, that TRH also has a role as a neuromodulator within the autonomous nervous system. In this study we analyzed the effects following peripheral administration of TRH (200 micrograms, 400 micrograms) in patients with endocrinological disorders and in healthy females and males. By means of a questionnaire, patients were asked about possible (side-) effects; ventilatory and cardiovascular monitoring was performed during steady state. The pulsatile TSH-secretion pattern was analyzed and thyroid and stress hormones were measured in the blood prior to and following TRH i.v. Frequent symptoms afer TRH were feeling of heat (58%), **stimulation of respiration (61%), palpitations (39%), micturition urge (52%) and restlessness (32%). Apparative monitoring demonstrated a short stimulation of respiration and an increase of heart rate. After 400 micrograms TRH i.v., blood levels of ACTH decreased slightly (p less than 0.01) but levels of T3, T4,** epinephrine, norepinephrine and cortisol remained unchanged (p greater than 0.05). TSH-levels were low during daytime and showed a surge at night.

Am J Cardiol 1994 Feb 15;73(5):374-8. **Usefulness of L-thyroxine to improve cardiac and exercise performance in idiopathic dilated cardiomyopathy.** Moruzzi P, Doria E, Agostoni PG, Capacchione V, Sganzerla P. "The short-term effects of L-thyroxine (100 micrograms/day, 10 patients) and placebo (10 patients) on idiopathic dilated cardiomyopathy were compared." **"A decrease in resting**

systemic vascular resistances and an increase in cardiac output ($p < 0.05$) were also observed. Cardiopulmonary effort parameters improved ($p < 0.05$) without hemodynamic changes at peak exercise. It is concluded that L-thyroxine short-term administration improves cardiac and exercise performance in patients with chronic heart failure, without modifying the adrenergic support to the heart and the circulatory parameters at peak exercise."

J Steroid Biochem 1983 Jul;19(1B):433-8. **Effects of anterior pituitary hormones and their releasing hormones on physiological and behavioral functions in rats.** Lin MT, Ho LT, Uang WN "The effects of direct administration of TRH, TSH, LHRH, LH, ACTH, GH, FSH and prolactin into cerebral ventricle system on metabolic, respiratory, cardiovascular and behavioral responses were assessed in unanesthetized rats, **Intraventricular administration of TRH, TSH, LHRH or LH caused hypothermia, decreased metabolism and/or cutaneous vasodilation at room temperature (22 degrees C)."** "In addition, intraventricular administration of TRH, LHRH or LH caused tachycardia, hypertension and a reduction in the epinephrine-induced reflex bradycardia." "Furthermore, following intraventricular administration of **TRH, but not TSH, LHRH, LH, FSH, GH, ACTH or prolactin three main categories of behavior were provoked: activity of normal type--forward locomotion stimulation, head and body rearing; stereotype activity--increased grooming and head swaying; and abnormal type behavior--tail elevation and piloerection in rats."**

Indian J Physiol Pharmacol 1984 Apr-Jun;28(2):153-8 **A study of pituitary-thyroid function during exercise in man.** Sawhney RC, Malhotra AS, Gupta RB, Rai RM "Exercise induced modulations in circulatory T4, T3 and TSH were monitored in 14 healthy euthyroid male volunteers undergoing exercise on a bicycle ergometer at 750 KPM for 20 minutes." "Serum T4 exhibited a significant decrease (P less than 0.05) from 9.6 +/- 0.49 microgram/dl (mean +/- SE) to 8.3 +/- 0.47 microgram/dl at 20 min after the termination of the exercise, whereas a significant decrease (P less than 0.01) in T3 levels from 158 +/- 9 ng/dl to 144 +/- 8.2 ng/dl was recorded at 40 min after the termination of the exercise." "These observations suggest that hormone **secretion by the thyroid and its responsiveness to endogenous TSH are maintained after exercise. The decrease in circulatory T4 and T3 could be due to an increase in degradation of the hormones or may reflect a generalized adaptation phenomenon. The exact mechanism and significance of these alterations remains to be elucidated."**

Arch Intern Med 1984 Jun;144(6):1149-52 **Diagnostic dosages of protirelin (TRH) elevate BP by noncatecholamine mechanisms.** Zaloga GP, Chernow B, Zajtchuk R, Chin R, Rainey TG, Lake CR "While performing thyroid function tests, we noticed that protirelin (TRH) raised BP, and, therefore, we investigated the effect of diagnostic dosages of protirelin (500 micrograms) on plasma catecholamine levels and cardiovascular function in eight patients one day before, one day after, and four weeks following heart surgery. **Mean arterial pressure (MAP), heart rate (HR), plasma norepinephrine (NE), epinephrine (EPI), dopamine (DA), thyroid hormone (triiodothyronine [T3], thyroxine), and thyrotropin (TSH) levels were measured before and after the intravenous injection of protirelin. Protirelin increased MAP transiently from 88 +/- 2 to 103 +/- 3 mm Hg (before surgery), 86 +/- 4 to 102 +/- 4 mm Hg (one day after surgery), and 86 +/- 4 to 104 +/- 5 mm Hg (four weeks after surgery)."** "We conclude the following: (1) **diagnostic dosages of protirelin transiently elevate MAP and SVR by a noncatecholamine mechanism, (2) clinicians who perform protirelin tests should be aware of protirelin's transient pressor effects."**

Endocrinologie 1982 Jul-Sep;20(3):165-76. **Endocrine circadian time structure in the aged.** Nicolau GY, Haus E, Lakatua DJ, Bogdan C, Petrescu E, Sackett-Lundeen L, Berg HG, Ioanitiu D, Popescu M, Chioran C "Thirteen circadian rhythms in plasma hormone levels (ACTH, aldosterone, cortisol, C-peptide, insulin, DHEA-S, estradiol, LH, prolactin, 17-OH progesterone, testosterone, T4 and TSH) were studied in April 1981 in 25 males and 25 females 57 to 91 years of age, institutionalized at the Berceni Hospital for the aged." "In comparison with previous data from the Endocrine Rhythms Laboratory ("C. I. Parhon" Institute) and series of younger subjects studied in Minnesota (St. Paul-Ramsey Medical Center) as well as in comparison with data published from other centers, the aged **seem to experience an earlier arousal of their endocrine system which may be related to certain disturbances of old age e.g. of sleep."**

Clin Endocrinol (Oxf) 1988 Jul;29(1):63-75. **A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism.** Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg PA, Lindstedt G. "Twenty women, who had been randomly selected from women with subclinical hypothyroidism identified in a population study were treated with L-thyroxine and placebo in a double-blind cross-over design during 2 x 6 months." "Heart rate-corrected preejection period and symptom score **decreased (P less than 0.05). Four women starting with L-thyroxine showed a marked and prolonged (4-6 months) rise in thyrotrophin concentration during the subsequent placebo period, but remained clinically euthyroid." "Subclinical hypothyroidism is common among middle-aged and old women, and our findings indicate that approximately one woman in four with this 'subclinical' condition will benefit from L-thyroxine treatment."**

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Ray Peat's Newsletter

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Sketch of some of the broader concepts needed in aging theory:

Estrogen increases with aging, and the characteristic changes of aging---including menopause, glucose intolerance/insulin resistance, autoimmunity and inflammatory dysregulation, respiratory decline, susceptibility to cancer, connective tissue hardening and slowed cellular responses---are produced by prolonged exposure to estrogen.

Radiation, cholera toxin, and a variety of stressors synergize with or imitate estrogen.

Estrogen is just one of the intrinsic excitatory substances, which are produced by stress, and which participate in self-stimulating loops.

Energy depletion, free-radical generation, and gene mutations are produced by estrogen and by the nitric oxide (NO) promoted by estrogen.

Estrogen and nitric oxide activate the pituitary, in just one of many vicious circles of self-stimulation.

Carbon dioxide produced in the high energy state provides direct protection of protein structure against random chemical changes. These protective effects occur within cells, between cells, and in the extracellular "ground substance" or matrix, in which cells are embedded. Thyroid and progesterone support CO2's protective effects.

Ammonia is one of the factors promoted by estrogen and other stressors, in competition with carbon dioxide.

Ammonia is pro-inflammatory. With NO (nitric oxide), TNF (tumor necrosis factor), glutamate, and calcium, it activates cells while interfering with their energy. *In vitro*, ammonia and lactate clearly poison cells (contributing to the myth of "programmed aging.")

The "little mouse," and the experiments of Denckla and Everitt, show that a simple growth hormone deficiency or lack of pituitary function can double the life span. Intervention in the many other self-stimulating excitatory pathways can produce additional retardation of the aging process, acting at many levels, from the extracellular matrix to the brain.

Estrogen, Aging, Radiation, Migraine & Energy

The Manhattan Project demonstrated that, by spending a couple of billion dollars, a very impressive explosion could be created by exploiting the unsurprising fact that, in the presence of a sufficient mass of suitable material, spontaneous radioactivity becomes self-stimulating. Part of the taxpayers' money was spent on convincing the public that the bomb was a natural outcome of the fundamentally humanistic scientific enterprise which would give everyone free electricity and a generally glorious life.

Now that we have genetically modified foods, and gamma-irradiated meats and vegetables, maybe it's time to evaluate the process that has led us to these technologies. By seeing how we arrived at our present scientific-technological state, I think many seemingly unrelated scientific and medical issues will take on new meaning, and I think this historical context will justify some reorientations in therapy.

Albert Einstein's name is often associated with the Manhattan Project, but years earlier he departed from the statistical world-view, the assumption of metaphysical randomness, that has characterized "quantum physics," as well as nuclear physics. During the years in which metaphysical randomness took over official physics, that world-view was also being applied to genetics. Eugenics and Racial Hygiene reached their peak almost simultaneously with the realization of the Atomic Bomb (or Tomic Bomb, as F. Soddy more correctly called it). Precisely the same mathematical formulas were used to describe nuclear fission and genetic mutation.

Young physicists from the Manhattan Project, with government financing, smoothly made a transition into genetics, becoming, almost

mysteriously, leaders in the field of "molecular biology." Government subsidies for the nuclear power industry were becoming government subsidies for the industrialization of biology.

The prestige of their background as Manhattan Project physicists made it unnecessary for them to learn anything about biology. As their institutes of molecular biology took over biology departments in the 1960s, they were able to control what was being taught to both undergraduate and graduate biology students.

The physics and physical chemistry that were really relevant to biology, that had been developed before the government/industry consortium took over, were effectively suppressed. If old science journals and monographs didn't just disappear, they were put into "storage," where they couldn't be browsed. At UCLA, for example, you have to place an order for a specific journal, and then wait days for someone to search for the book. Computerized data-bases simply ignored the older work, even though the volume of research published throughout the world in 1930 or 1950 would be similar to the amount currently published in a week or month.

The head of Oregon's Institute of Molecular Biology argued that science develops by its own logic, and can't be blamed for the anti-humanistic ways in which it is used. Since, as a Manhattan Project physicist, he didn't have any knowledge of biology or of other branches of physical science, he couldn't be aware of the powerful ways in which science was distorted by industrial and military intervention. Science, as an ideal, of course can't be blamed for the anti-scientific absurdities that have been sold to the public in the name of science.

First, a philosophy of atomistic reductionism told people that they must give up ideas of teleology, anthropomorphism, purpose, direction, consciousness, and holism, as archaic metaphysical and unscientific concepts. Then, in this cultural vacuum, it was possible to impose the metaphysic of control and of technological improvement, an accountant's metaphysics of the bottom line, which always looks for the quickest return and the most discrete result. The doctrine of genetic determinism was intrinsic to the Eugenics movement: The proper authorities could improve the race by killing the inferior specimens, because it is in the (random) nature of the world that things would degenerate if the fit weren't preserved and the unfit destroyed. The mathematical treatment of random events has no place for the complexities of context, and so is perfect for a system in which the only issue is the power to control for an immediate benefit. Ecology and physiology were marginalized by their very complexity.

These doctrines of random mutation, and of "hygienically" killing the deviant cells, took over cancer biology, with governmental financing.

There was no shortage of evidence that contradicted the idea that cancer arises as a single mutant cell, but few people are now aware of that evidence. Harry Rubin is one of the few people remaining who understand the evidence, and build on it.

The definition of a gene has been revised many times. Originally, a gene was something that produced "a trait," and then it was said to be the "functional unit of heredity." Currently, it is often stated as "the section of DNA that contains the information for making a functonal biological product, which may be a protein or an RNA molecule." But, informally, the traditional view is often passed on, leading many people to think that each protein has "its gene."

The dogmatic view (once taught by molecular geneticists) that "one gene produces one protein" has falsified everything in biology: In reality, the environmentally responsive changes in the composition of proteins means that there are a multitude of different "growth hormones," "prolactins," "interleukins," "hormone receptors," etc. Stress and aging cause cumulative deviations through this process of chemical differentiation.

Rather than seeing cancer (or aging or various degenerative diseases) as a special problem in developmental biology, governed by complex interactions of cells with their environment, **the doctrine of the deviant mutant cell has become an excuse for gross biological ignorance.**

Chronic irritation used to be emphasized as a cause of cancer, but all of the irritating factors were reduced to mutagenic factors, and this made it possible to devalue the tissue changes produced by chronic injury, which preceded and accompanied the development of cancer.

Tissue fibrosis, which was associated with both inflammation and atrophy of injured tissues, became separated from the study of cancer, because it was a complex physiological process, and not a distinct genetic event.

But changes in the connective tissue matrix were always crucially involved in the process of cancerization, and these changes overlapped with the changes that could be seen in many other biological processes.

Ionizing radiation produces inflammation, edema, over-production of collagen, and finally atrophy and fibrosis, with hardening of the collagen and slowing of repair processes. In the atrophic tissue, cancer sometimes develops. Many other harmful agents produce very similar sequences of tissue changes--heat, suffocation, malnutrition, chemical poisoning, and estrogen excess, for example.

The role of the balanced, or imbalanced, tissue environment in carcinogenesis can be seen very clearly in an experiment in which small sheets of plastic were implanted in animals. Near some of the sheets, nests of cancer cells would develop, but they always developed in a concavity that had been formed by the folding of the plastic sheet, almost isolating some cells from their normal environment. This experiment was reminiscent of the experiments of Hans Selye's, in which he found that the tissue which had grown into small subcutaneously implanted glass tubes aged much more rapidly than the rest of the animal's tissues.

The changes of aging are so similar to those of radiation damage that some people have believed that aging was caused by environmental radiation, or at least that radiation accelerates normal aging. The first isn't true, the second is probably approximately true. Anything that produces inflammation, increasing collagen production and collagen hardening, and that slows tissue renewal, is accelerating changes that seem characteristic of aging. But the idea that radiation produces aging by creating mutations has been very clearly refuted. Molecular biologists generally lost interest in the age-accelerating effects of raditation when they saw it wasn't acting through genetic mutations.

Ultraviolet damage to the skin causes changes in the extracellular connective substance that are very similar to aging, but that can be distinguished from the normal age changes by slight differences in the chemistry of the cross-links that make the tissue more rigid. For practical purposes, though, the similarities are more important than the differences.

The "collagen theory of aging" was the idea that the changes which occur in the extracellular matrix (of which collagen is only one component) lead to progressive changes in cellular metabolism, shutting off their access to the blood stream, and that these changes in the matrix are the essential cause of aging. The differences in thickness and flexibility between tanned cowhide and calf-skin, the toughness of meat from old animals, and the rigidity of ligaments in old joints make it obvious that connective tissue changes are characteristic of aging.

Some people who advocate the collagen theory of aging believe that the cross-links that accumulate with age are mainly produced by free radicals (which may be derived from peroxidized lipids, heavy metals, radiation, or ascorbic acid, for example), but others emphasize the role of glucose in forming the links, since diabetes accelerates the hardening of collagen.

In scar tissue, calluses, keloids, and oil granulomas or allergic granulomas, tissue injury or stress has produced structural changes. Tissue stress affects the structure of connective tissues very generally. Tendons and bones are guided and altered in their development by pressure and tension. Histologists have said that they can distinguish structural differences in the bones of wild animals and tame animals of the same species, apparently resulting from the differences in their way of life.

Cellular and extracellular responses are interactive, so that stressed cells produce defective extracellular matrix, which can contribute to the stress of the cells. Changes induced by stress in

some cases interfere with the proper differentiation of cells regulated by their extracellular matrix.

In early studies of estrogen-treated animals, estrogen was found to cause tremendous increases in the deposition of collagen. In the 1960s, detailed studies on the hardening of tendons with aging were done. **It was discovered that estrogen treatment accelerated the stiffening of tendons that normally occurs with aging,** and that progesterone reversed the estrogen effect.

On the level of the whole organism, stress causes overactivity of the pituitary, **and removal of the pituitary extends life, and retards the hardening of the extracellular connective material (Everitt, et al., 1983). The collagen theory of aging necessarily involves the endocrine system.**

When I was measuring the oxygen consumption of uterine tissue from animals of different ages, I found that tissue from some of the oldest animals had what appeared to be "negative oxygen consumption," that is, some gas was being produced at a higher rate than oxygen was being produced, increasing the volume or pressure of the air in the chamber, instead of decreasing it. Since I knew that fatigued nerve and muscle emit some ammonia, I arranged my experiment so that both carbon dioxide and ammonia would be absorbed from the air, and found that these tissues were actually consuming oxygen at a much higher rate than tissues from young animals. While the uterus of a young animal is flexible and bright pink, the uterus from a typical old animal was stiff and purple or blue, indicating an oxygen deficiency. Apparently, their high rate of oxygen consumption was creating a relatively hypoxic condition in the aged uterus. (The rest of my research had to do with identifying the nature of this oxygen consumption; estrogen stimulates the "NADH-oxidase" enzyme function, which---like age-pigment itself---can create a short-circuit between oxygen and the NADH energy source. This serves the purpose of allowing glycolysis to continue in the absence of normal mitochondrial functioning, and probably interferes with normal mitochondrial production of ATP, CO_2, etc., by competing for the oxygen supply.)

Estrogen is known to decrease liver glycogen storage, while progesterone increases it. If a tissue is stimulated to metabolize at a high rate, especially without an adequate supply of glucose, it will consume protein as fuel, with the production of ammonia. Apparently, what I saw in my experiments with the old uteri was a consequence of combining a high level of stimulation with a low level of glucose and oxygen. In nerves, this would be called excitotoxicity.

Although there are several ways in which estrogen can increase the formation of ammonia, just producing hypoxia is sufficient to cause a large increase in ammonia production. **Any exaggerated stimulation, stress, or energy deficit tends to increase the level of ammonia in tissue.** Because of the association of ammonia with energy depletion, many people argue that the ammonia released from nerve and muscle comes primarily from the breakdown of ATP, leading to the deamination of adenosine. But by 1970 there was already clear evidence for other important sources of ammonia. The use of amino acids for fuel, which happens during stress, releases ammonia. **Eating isolated amino acids, exercising intensely, or having an excess of cortisol, causes tissue proteins to be broken down, with the release of ammonia.** Although the free amino acid, glutamate, can be combined with ammonia to remove it safely from cells, ammonia can also be combined with the glutamic acid (or aspartic acid) groups in tissue proteins. **This binding of ammonia to an acid is called amidation.**

When I have written about the importance of carbon dioxide, I mentioned that it binds to amino groups (often lysine) in proteins, protecting those groups from combination with sugars (glycosylation) or the products of lipid peroxidation. Peptide hormones and antibodies function very differently when they have been glycosylated. The lysine groups, that are so important for carbon dioxide's protective effects, are important sites for the cross-linking reactions in collagen, and one form of cross-linking involves the connection of a glutamine group in one protein with the lysine group in another.

Amidation and deamidation occur fairly massively during fatigue and rest in brain proteins, and in many other systems. The activities of proteins are changed as a consequence, but there has been very little research into this important area, because the dogma that "one gene produces one protein" has created the sense that there is something unwholesome about these protein-modifying complexities. Nevertheless, **it is clear that inflammation, connective tissue aging, keratinization, and antigenic changes of tissues and proteins (relevant to autoimmunity and "connective tissue diseases" as well as normal development) are influenced by amidation.**

Estrogen causes epithelial cells to cornify or keratinize (condensing, and being converted mainly into the "horny" material, keratin) earlier than they would otherwise. This process of final differentiation normally occurs as the cells of the skin or mucous membrane grow outward, away from the blood vessels that supply them with nutrients and oxygen. Simply growing away from their supporting blood vessels creates a stress of deprivation. Vitamin A is one of the factors that opposes estrogen and prevents premature keratinization of epithelial cells.

The same enzymes that keratinize cells under the influence of estrogen, and that participate in the solidification of blood clots and the contraction of connetive tissue in healing wounds, can also cross-link collagen molecules.

One of the molecules forming the crosslink bond is glutamine, which exists normally in proteins, but which can also be formed by the addition of ammonia to the acidic side-chain of glutamic acid. The other amino acid that reacts to form the cross-link bond is lysine, which can be protected against chemical reactions by combining with carbon dioxide, This protective effect of carbon dioxide is probably as widely distributed as is lysine in protein, though even when a lysine group isn't exposed, all proteins have an amino group at one end that can interact with carbon dioxide or other substance. **Hormones and their "receptors," enzymes, and structural proteins all exist in multiple forms. The genetic dogma that "one gene corresponds to one protein" has been extremely misleading, and has allowed most researchers to ignore the processes that dominate physiological adaptation.**

Oxygen deprivation is enough to stimulate collagen synthesis (Chvapil; 1968, 1969, 1975), and is probably one of the common factors in tissue degeneration. **Estrogen excess tends to reduce the availability of oxygen in tissues, and oxygen deprivation in many cases imitates estrogenic stimulation.** .The ammonia produced in stressed tissues contributes to changes in collagen and the extracellular matrix, and has both local and systemic effects.

Ammonia, like estrogen, promotes the excitotoxic processes, activating the production of nitric oxide (NO), and stimulating the glutamate receptors, sometimes causing seizures, and if prolonged, causing stupor or coma. But it always activates the pituitary, and in other tissues, the production of free radicals causes molecular tissue damage. The stressors produced by estrogen, for example NO and growth hormone, activate the enzyme aromatase, which synthesizes estrogen, in just one of the many vicious circles. Growth hormone tends to increase ammonia levels.

Estrogen is just one of the intrinsic excitatory substances, which are produced by stress, and which participate in self-stimulating loops. Ammonia and nitric oxide are two of the most pervasive endogenous excitants and toxins. "NO [nitric oxide] is emerging as an important endogenously-derived neurotoxin" (Dawson and Dawson, 1995).

Ammonia, like nitric oxide, inhibits respiration, and can increase the Crabtree effect (with aerobic glycolysis stimulated by increased glucose, inhibiting respiration). This suggests an important role for it in cancer in general, and especially in liver cancer. In the uncontrolled glycolysis of cancer, ammonia can be used to form amino acids from the lactate and pyruvate produced by glycolysis, supporting growth of the tumor at the expense of the normal tissues that are producing ammonia by protein degradation.

Ammonia can produce both convulsive seizures and stupor or coma, and it alters brain

cells, shifting the balance toward that seen in Alzheimer's disease.

Ammonia contributes to the hypertrophy of damaged kidneys, and the same mechanism, decreased protein breakdown in the presence of too much ammonia, probably contributes to the increased volume of extracellular matrix that occurs in so many diseases of stress, aging, and hyperestrogenism.

Ammonia has also been found to be increased during migraine attacks. I suspect that progesterone's sometimes dramatic effect on migraine involves ammonia and energy metabolism. Ammonia disturbs carbon dioxide's regulation of brain circulation, and when ammonia is "detoxified" into glutamine (though glutamine is still toxic in excess) ATP is consumed, leading to dysregulation of vascular smooth muscle. Progesterone's ability to stop the local excitation of nerve cells spares ATP. It seems likely that nitric oxide, the production of which is inhibited by progesterone, is also involved in the vasodilation and energy depletion.

Almost any sort of liver disease increases the systemic ammonia level. Estrogen can cause a large variety of liver diseases, including fatty liver and cholestasis; ammonia, which is toxic in itself, also links into another potentially toxic system, the porphyrin synthetic system.

Porphyria (acute intermittent porphyria, hepatic porphyria) is a disease that can cause nerve damage, hypertension, and connective tissue damage. It typically involves an excess of two precursors of heme, and sometimes a deficiency of heme (needed for respiratory enzymes), and it is often triggered by hypoglycemia, by exercise, and by estrogen or by certain poisons. Although it is usually described as a strictly genetic disease, it is highly susceptible to environmental influences, and a proper reevaluation of the evidence might show that it is more often environmental than genetic. Most of the evidence for a genetic cause consists of measurements that show low activity of certain enzymes. Since the conditions prevailing when a protein is synthesized can affect its structure and functions, the simple measurement of enzyme activity is hardly an appropriate argument.

The two substances that accumulate happen to be in a synthetic sequence, subsequent to a step in which CO2 is removed, and before a step in which NH3, ammonia, is removed. The principle of mass action indicates that a reaction will slow or stop when there is a certain concentration of the product of the reaction. High CO2 and low NH3 will prevent an accumulation of these chemicals, one of which is a potent neurotoxin. The opposite situation, low CO2 and high NH3 (ammonia), will tend to cause an accumulation of these substances. Therefore, a simple metabolic shift that predictably happens in stress and malnutrition, can explain the main type of porphyria, independently of specific genetic problems. Everyone's genetic constitution is unique, and in a metabolically complex condition such as porphyria, there will be a spectrum of susceptibility. To draw a line across the spectrum, dividing people with "genetic defects" from the normal, is a purely arbitary and illogical procedure. It is much more important to identify and eliminate "porphyriogenic" environments.

Since porphyria attacks commonly occur premenstrually or after skipping a meal, the food cravings caused by increased estrogen and lowered blood sugar, are probably reinforced in many people by dread of the terrible symptoms that can be produced by not eating enough, resulting from the increased ammonia and porphyrins or porphyrin precursors. Calorie restriction can be dangerous when porphyria is developing.

The presence of porphyrin poisoning, with its associated free radical toxins, can lead to the activation of heme oxygenase, the enzyme which produces carbon monoxide, which I have discussed elsewhere as a cause of the respiratory defect that characterizes cancer. Both ammonia and porphyria have been implicated in the production of cancer.

Acetazolamide, a drug that causes carbon dioxide to be retained in the tissues, tends to block the formation of ammonia. This is probably a confirmation of the importance of carbon dioxide as an anti-ammonia factor. High altitude also causes increased retention of carbon dioxide in the tissues, because of the Haldane-Bohr effect,

and the reduction of ammonia (production, serum concentration, and excretion) at high altitude is probably even greater than the reduction of lactate production.

Fibrotic tissue can be repaired, and the essential thing is to interrupt the processes that caused it to develop. I have written previously about the effects of vitamin E, progesterone, and DHEA on scars, keloids, scleroderma, arthritis, and liver cirrhosis, but there are many helpful therapies. Saturated fats are extremely important in the reversal of fibrosis. Recently, it has been found that just covering a keloid with a layer of silicone causes it to regress to some extent. I think the sealant allows carbon dioxide to accumulate, shifting the balance away from growth and toward shrinkage of the collagenous mass.

The particular therapy that's most helpful will depend on the particular nature of the stressor, but good nutrition is always of the greatest importance. Carnitine protects against ammonia; adenosine, niacin, and caffeine protect against various types of excitotoxicity. Vitamin A protects against premature cornification, and probably other cross-linking. Thyroid, progesterone, and glucose help to minimize exaggerated protein catabolism, and magnesium has a great variety of restorative functions.

Carnitine has been used with sodium benzoate and phenylacetate to lower ammonia, but the latter can produce some side effects. Except for treating neurotoxic ammonia, I don't recommend use of carnitine supplementation, since there is good evidence that carnitine increases oxidative damage when there is an abundance of unsaturated fat in the organism. Aspirin's similarity to benzoate and phenylacetate suggests that it might sometimes help to remove ammonia. The safest procedure is to use foods, such as fruit juices, that regulate nitrogen metabolism in varied ways.

The alpha-keto acids, which are found in many fruits, can bind ammonia, becoming ordinary amino acids. Potato juice (eliminating the starch with a carrot juicer) is a rich source of these alpha-keto acids.

Estrogen increases fairly steadily with aging in men, and its effects become more harmful as testosterone and other protective antiestrogens decline with aging. In women, the absolute estrogen level rises until near menopause, but during those years very high levels of progesterone protect most women against its harmful effects. The diseases that affect women more often than men are mainly diseases caused by a failure of progesterone and thryoid to regulate estrogen. The generally greater resistance and longevity of women can be attributed largely to progesterone dominance over estrogen. The extremely high progesterone production during pregnancy probably has long lasting protective effects, since there is clear evidence that longevity increases with the number of children borne. In animals, a large number of pregnancies produces anti-aging, and anti-estrogenic, effects that can be seen even in the elasticity of tendons.

The amount of irradiation needed to extend the shelf life of food is around 100,000 rads to 300,000 rads or even more, and even that intensity can't overcome the problem of dirty production facilities. **This amount of radiation produces a large amount of ammonia in food.** Dogs fed meat that had been irradiated were found to have severely depressed essential amino acids, and a low level of magnesium, protein, and creatinine in the blood. Vitamin A and other nutrients were depleted.

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Ray Peat's Newsletter

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MAIN IDEAS AND CONTEXTS

***Lactic acid and carbon dioxide** have opposing effects.*

***Intense exercise damages** cells in ways that cumulatively impair metabolism. There is clear evidence that glycolysis, producing lactic acid from glucose, has toxic effects, suppressing respiration and killing cells. Within five minutes, exercise lowers the activity of enzymes that oxidize glucose. Diabetes, Alzheimer's disease, and general aging involve increased lactic acid production and accumulated metabolic (mitochondrial) damage.*

***The products of glycolysis**, lactic acid and pyruvic acid, suppress oxidation of glucose.*

***Adaptation** to hypoxia or increased carbon dioxide limits the formation of lactic acid. Muscles are 50% more efficient in the adapted state; glucose, which forms more carbon dioxide than fat does when oxidized,, is metabolized more efficiently than fats, requiring less oxygen.*

***Lactic acidosis**, by suppressing oxidation of glucose, increases oxidation of fats, further suppressing glucose oxidation.*

***Estrogen** is harmful to mitochondria, **progesterone** is beneficial.*

***Progesterone's brain-protective** and restorative effects involve mitochondrial actions.*

***Thyroid hormone, palmitic acid, and light** activate a crucial respiratory enzyme, suppressing the formation of lactic acid. Palmitic acid occurs in coconut oil, and is formed naturally in animal tissues. Unsaturated oils have the opposite effect.*

***Heart failure, shock**, and other problems involving excess lactic acid can be treated "successfully" by poisoning glycolysis with dichloroacetic acid, reducing the production of lactic acid, increasing the oxidation of glucose, and increasing cellular ATP concentration. Thyroid, vitamin B1, biotin, etc., do the same.*

B1

Mitochondria and mortality: Diet, exercise, and medicine, damaging or repairing respiratory metabolism

Since reading Warburg's publications in the late 1960s and early 70s, and doing my own research on tissue respiration, I have been convinced that Warbug was on the right track in seeing mitochondrial respiration as the controlling influence in cell differentiation, and in seeing cancer as a reversion to a primitive form of life based on a "respiratory defect." Harry Rubin's studies of cells in culture have expanded Warburg's picture of the process of cancerization, showing that genetic changes occur only after the cells have been transformed into cancer.

It is now well recognized that defective mitochondrial respiration is a central factor in diseases of muscles, brain, liver, kidneys, and other organs. The common view has been that the mitochondrial defects are produced by genetic defects, that are either inherited or acquired, and are irreversible.

Mitochondria depend on some genes in the nuclear chromosomes, but they also contain some genes, and mutations in these specific mitochondrial genes have been associated with various diseases, and with aging. Although these aren't the genes that the cancer establishment has focussed on as "the cause" of cancer, for people interested in the achievements of Warburg and Rubin, it is important to know whether mutations in these mitochondrial genes are the *cause* of respiratory defects, or whether a respiratory defect causes the mutations. Recent research seems to show that physiological problems precede and cause the mutations.

Warburg believed that mitochondria supported specialized cell functions by concentrating themselves in the places where energy is needed. This idea has some interesting implications. For example, when the amount of thyroid hormone is increased, or when the organism adapts to a high altitude, the number of mitochondria increases. But in energy deficient states such as diabetes, they don't. How are these crucial organelles called into existence by the hormone that increases respiration and energy, and also by the hypoxic conditions of high altitudes? In both of these conditions, the availability of oxygen is limiting the ability to produce energy. In both conditions, carbon dioxide concentration in tissue is higher, in one case, because thyroid stimulates its production, in the other, because the Haldane effect limits its loss from the lungs.

SOME DEFINITIONS

Glycolysis: The conversion of glucose to lactic acid, providing some usable energy, but many times less than oxidation provides.

***Lactic acid,** produced by splitting glucose to pyruvic acid followed by its reduction, is associated with calcium uptake and nitric oxide production, depletes energy, contributing to cell death.*

***Crabtree effect:** Inhibition of cellular respiration by an excess of glucose; excess of glucose promotes calcium uptake by cells.*

***Pasteur effect:** Inhibition of glycolysis (fermentation) by oxygen.*

***Randle effect:** The inhibition of the oxidation of glucose by an excess of fatty acids. This lowers metabolic efficiency. Estrogen promotes this effect.*

***Lactated Ringer's solution:** A salt solution that has been used to increase blood volume in treating shock; the lactate was apparently chosen as a buffer in place of bicarbonate as a matter of convenience rather than physiology. This solution is toxic, partly because it contains the form of lactate produced by bacteria, but our own lactate, at higher concentrations, produces the same sorts of toxic effect, damaging mitochondria.*

***Estrogenic phytotoxins** damage mitochondria, kill brain cells; tofu is associated with dementia.*

Could carbon dioxide, a major product of mitochondria, help to call mitochondria into existence? My answer to this is "yes," and it will help to briefly explain how I see mitochondria. Although I have no hesitancy in accepting that organelles can be exchanged between species, and that it is conceivable that mitochondria might have been derived from symbiotic bacteria, I am reluctant to believe that something happens just because it *could* happen. For example, Francis Crick proposed that life on earth originated when genes arrived here on space dust from some other world. That's a theoretical possibility, but what's the point? It just avoids explaining how the highly organized material came into existence somewhere else, and it probably seriously interfered with the consideration of the ways life could arise here. Similarly, some people like to think that mitochondria and chloroplasts were originally bacteria, that came into symbiosis with another kind of living material, consisting of nucleus and cytoplasm. Like Crick's "space germs," it can be argued that it's possible, but the problem is that this explanation can stop people from thinking freshly about the nature of the various organelles, and how they came to exist. (How did cells originate? How did mitochondria originate? "Germs.")

Since I have a view of how cells came to exist, under conditions that exist on earth, I should consider whether that view doesn't also reasonably account for their various components. Sidney Fox's proteinoid microspheres provide a good model for the spontaneous formation of primitive cells; variations of that idea can account for the formation of organelles (such as mitochondria and nuclei within cells, and chromosomes within nuclei). The value of this idea, of a self-stimulating process in mitochondrial generation, is that it suggests many ways to test the idea experimentally, and it suggests explanations for developmental and pathological processes that otherwise would have no coherent explanation.

Proteinoid microspheres and coacervates form by acquiring molecules from solution, condensing them into a separate phase, with its own physical properties. At every phase boundary, there are numerous physical forces, especially electronic properties, that make each kind of interface different from other kinds. Small changes of pH, temperature, of salts and other solutes can alter the interfacial forces, causing particles to dissolve,

or grow, or fragment, or to move. In the way that carbon dioxide alters the shapes and electrical affinities of hemoglobin and other proteins, I propose that it increases the stability of the mitochondrial coacervate, causing it to "recruit" additional proteins from its external environment, as well as from its own synthetic machinery, to enlarge both its structure and its functions.

In the relative absence of carbon dioxide, or excess of alternative solutes and adsorbents, such as lactic acid, the stability of the mitochondrial phase would be decreased, and the mitochondria would be degraded in both structure and function. As the back side of the idea that carbon dioxide stabilizes and activates mitochondria, the idea that lactic acid is involved in the degrading of mitochondria can also be tested experimentally, and it is already supported by a considerable amount of circumstantial evidence.

This combination of sensitivity to the environment, with a kind of positive feedback or inertia either upward or downward, corresponds to what we actually see in mitochondrial physiology and pathology.

The Crabtree effect, which is the suppression of respiration by glycolysis, is often described as the simple opposite of the Pasteur effect, in which respiration limits glycolysis to the rate that allows its product to be consumed oxidatively. But the Pasteur effect is a normal sort of control system; when the Pasteur effect fails, as in cancer, there is glycolysis which is relatively independent of respiration, causing sugar to be consumed inefficiently. Embryonic tissues sometimes behave in this manner, leading to the suggestion that glycolysis is closely related to growth. Unlike the logical Pasteur effect, the Crabtree effect tends to lower cellular energy and adaptability. Looking at many situations in which increasing the glucose supply increases lactic acid production and suppresses respiration, leading to maladaptive decrease in cellular energy, I have begun thinking of lactic acid as a toxin. The use of Ringer's lactate solution in medicine has led many people to assume that lactate must be beneficial, or they wouldn't put it in the salt solution that is often used in emergiencies; however, I think its use here, as a buffer, is simply a convenience, because of the instability of some bicarbonate solutions.

On the organismic level, it is clear that lactic acid is "the essence of hyperventilation," and that it produces edema and malfunction on a grand scale: The panic reaction, shock lung, vascular leakiness, brain swelling, and finally multiple organ failure, all can be traced to an excess of lactic acid, and the related features of hyperventilated physiology.

Otto Warburg apparently thought of lactate as simply a sign of the respiratory defect that characterizes cancer. V. S. Shapot at least hinted at its possible role in turning on the catabolic reactions leading to cancer cachexia (wasting). I think a good case can be made for lactate as the *cause* of the respiratory defect in cancer, just as it is usually the immediate cause of the respiratory derangement of hyperventilation on the organismic level.

The Crabtree effect is usually thought of as just something that happens in tumors, and some tissues that are very active glycolytically, and some bacteria, when they are given large amounts of glucose. But when we consider lactate, which is produced by normal tissues when they are deprived of oxygen or are disturbed by a stress reaction, the Crabtree effect becomes a very general thing. The "respiratory defect" that we can see on the organismic level during hyperventilation, is very similar to the "systemic Crabtree effect" that happens during stress, in which respiration is shut down while glycolysis is activated. Since oxidative metabolism is many times more efficient for producing energy than glycolysis is, it is maladaptive to shut it down during stress.

Since the presence of lactate is so commonly considered to be a normal and adaptive response to stress, the shut-down of respiration in the presence of lactate is generally considered to be caused by something else, with lactate being seen as an effect rather than a cause. Nitric oxide and calcium excess have been identified as the main endogenous antirespiratory factors in stress, though free unsaturated fatty acids are clearly involved, too. However, glycolysis, and the products of glycolysis, lactate and pyruvate, have been found to have a causal role in the suppression of respiration; it is both a cause and a

consequence of the respiratory shutdown, though nitric oxide, calcium, and fatty acids are closely involved.

Since lactic acid is produced by the breakdown of glucose, a high level of lactate in the blood means that a large amount of sugar is being consumed; in response, the body mobilizes free fatty acids as an additional source of energy. An increase of free fatty acids suppresses the oxidation of glucose. (This is called the Randle effect, glucose-fatty acid cycle, substrate-competition cycle, etc.) Women, with higher estrogen and growth hormone, usually have more free fatty acids than men, and during exercise oxidize a higher proportion of fatty acids than men do. This fatty acid exposure "decreases glucose tolerance," and undoubtedly explains women's higher incidence of diabetes. While most fatty acids inhibit the oxidation of glucose without immediately inhibiting glycolysis, palmitic acid is unusual, in its inhibition of glycolysis and lactate production without inhibitng oxidation. I assume that this largely has to do with its important function in cardiolipin and cytochrome oxidase.

Exercise, like aging, obesity, and diabetes, increases the levels of circulating free fatty acids and lactate. But ordinary activity of an integral sort, activates the systems in an organized way, increasing carbon dioxide and circulation and efficiency. Different types of exercise have been identified as destructive or reparative to the mitochondria; "concentric" muscular work is said to be restorative to the mitochondria. As I understand it, this means contraction with a load, and relaxation without a load. The heart's contraction follows this principle, and this could explain the observation that heart mitochondria don't change in the course of ordinary aging.

When a person has an accident, or surgery, and goes into shock, the degree of lactic acidema is recognized as an indicator of the severity of the problem. Lactated Ringer's solution has been commonly used to treat these people, to restore their blood pressure. But when prompt treatment with lactated Ringer's solution has been compared with no early treatment at all, the patients who are not "rescuscitated" do better than those who got the early treatment. And when Ringer's lactate has been compared with various other solutions, synthetic starch solutions, synthetic hemoglobin polymer solution, or simply a concentrated solution of sodium chloride, those who received the lactate solution did least well. For example, of 8 animals treated with another solution, 8 survived, while among 8 treated with Ringer's lactate, 6 died.

Mitochondrial metabolism is now being seen as the basic problem in aging and several degenerative diseases. The tendency has been to see random genetic deterioration as the driving force behind mitochondrial aging. Genetic repair in mitochondria was assumed not to occur. However, recently two kinds of genetic repair have been demonstrated. One in which the DNA strand is repaired, and another, in which sound mitochondria are "recruited" to replace the defective, mutated, "old" mitochondria.

In ordinary nuclear chromosomal genes, DNA repair is well known. The other kind of repair, in which unmutated cells replace the genetically damaged cells, has been commonly observed in the skin of the face: During intense sun exposure, mutant cells accumulate; but after a period in which the skin hasn't been exposed to the damaging radiation, the skin is made up of healthy "young" cells.

In the way that the skin can be seen to recover from genetic damage, that had been considered to be permanent and cumulative, simply by avoiding the damaging factor, mitochondrial aging is coming to be seen as both avoidable and repairable.

The stressful conditions that physiologically harm mitochondria are now being seen as the probable cause for the mitochondrial genetic defects that accumulate with aging. Stressful exercise, which has been known to cause breakage of the nuclear chromosomes, is now seen to damage mitochondrial genes, too. Providing energy, while reducing stress, seems to be all it takes to reverse the accumulated mitochondrial genetic damage.

Fewer mitochondrial problems will be considered to be inherited, as we develop an integral view of the ways in which mitochondrial physiology is disrupted. Palmitic acid, which is a major

component of the cardiolipin which regulates the main respiratory enzyme, becomes displaced by polyunsaturated fats as aging progresses. Copper tends to be lost from this same enzyme system, and the state of the water is altered as the energetic processes change.

While the flow of carbon dioxide moves from the mitochondrion to the cytoplasm and beyond, tending to remove calcium from the mitochondrion and cell, the flow of lactate and other organic ions into the mitochondrion can produce calcium accumulation in the mitochondrion, during conditions in which carbon dioxide synthesis, and consequently urea synthesis, are depressed, and other synthetic processes are changed.

Glycolysis produces both pyruvate and lactate, and excessive pyruvate produces almost the same inhibitory effect as lactate; since the Crabtree effect involves nitric oxide and fatty acids as well as calcium, I think it is reasonable to look for the simplest sort of explanation, instead of trying to experimentally trace all the possible interactions of these substances; a simple physical competition between the products of glycolysis and carbon dioxide, for the binding sites, such as lysine, that would amount to a phase change in the mitochondrion. Glucose, and apparently glycolysis, are required for the production of nitric oxide, as for the accumulation of calcium, at least in some types of cell, and these coordinated changes, which lower energy production. could be produced by a reduction in carbon dioxide, in a physical change even more basic than the energy level represented by ATP The use of Krebs cycle substances in the synthesis of amino acids, and other products, would decrease the formation of CO2, creating a situation in which the system would have two possible states, one, the glycolytic stress state, and the other, the carbon dioxide producing energy-efficient state.

Besides the frequently discussed interactions of excessively accumulated iron with the unsaturated fatty acids, producing lipid peroxides and other toxins, the accumulated calcium very probably forms some insoluble soaps with the free fatty acids which are released even from intracellular fats during stress. The growth of new mitochondria probably occasionally leaves behind such useless materials, combining soaps, iron, and porphyrins remaining from damaged respiratory enzymes.

When the background of carbon dioxide is high, circulation and oxygenation tend to prevent the anaerobic glycolysis that produces toxic lactic acid, so that a given level of activity will be harmful or helpful, depending on the level of carbon dioxide being produced at rest.

Preventively, avoiding foods containing lactic acid, such as yogurt and sauerkraut, would be helpful, since bacterial lactic acid is much more toxic than the type that we form under stress. Avoiding the stress-promoting antithyroid unsaturated oils is extremely important. Their role in diabetes, cancer, and other age-related and degenerative diseases (and I think this includes the estrogen-promoted autoimmune diseases) is well established. Avoiding phytoestrogens and other things that increase estrogen exposure, such as protein deficiency, is important, because estrogen causes increased levels of free fatty acids, increases the tendency to metabolize them at the expense of glucose metabolism, increases the tissue content of unsaturated fatty acids, and inhibits thyroid functions.

Light promotes glucose oxidation, and is known to activate the key respiratory enzyme. Winter sickness (including lethargy and weight gain), and night stress, have to be included within the idea of the "respiratory defect," shifting to the antirespiratory production of lactic acid, and damaging the mitochondria.

Therapeutically, even powerful toxins that block the glycolytic enzymes can improve functions in a variety of organic disturbances "associated with" (caused by) excessive production of lactic acid. Unfortunately, the toxin that has become standard treatment for lactic acidosis--dichloroacetic acid--is a carcinogen, and eventually produces liver damage and acidosis. But several nontoxic therapies can do the same things: **Palmitate (formed from sugar under the influence of thyroid hormone, and found in coconut oil), vitamin B1, biotin, lipoic acid, carbon dioxide, thyroid, naloxone, acetazolamide, for example.** Progesterone, by blocking

estrogen's disruptive effects on the mitochondria, ranks along with thyroid and a diet free of polyunsaturate fats, for importance in mitochondrial maintenance.

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Ray Peat's Newsletter

Folly is the cloke of knavery.

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Estrogen's Mechanisms in Aging and Cancer

Estrogen is an important factor in aging and cancer, but the fact of its toxicity is systematically obscured, discouraging proper treatments.

If we want to understand what estrogen is, we should know what it does, and how it does it. Despite the drug industry's weekly releases to the mass media, explaining the wonderful consequences of "selectively activating the estrogen receptor," it isn't clear what estrogen does. It is, however, perfectly clear that estrogen doesn't do the things the industry says it does.

The industry's basic story was that estrogen is "the female hormone," and that supplementing it makes all of the female functions better, including fertility and pregnancy.

But in reality, supplemental estrogen masculinizes, sterilizes, promotes prostate cancer, kills embryos and fetuses, breaks chromosomes, disorganizes cell division, mutates genes, causes seizures, and shifts metabolic patterns.

One of estrogen's relatively normal effects is to shift metabolism toward the production of more lactic acid, and less ATP. Examining these relatively simple effects offers very interesting insights into what estrogen is.

Changing the cell's energy economy through modulation of enzymes is an important alternative to special receptor-mediated actions. This approach is probably the only one that can account for the estrogenic actions of oxygen deprivation and irradiation with x-rays or ultraviolet rays.

The right food, the right activity, the right air and the right light, supported when necessary by the right hormone or drug, can change the basic energy metabolism.

The idea of "estrogen dominance" in menopause has been accepted by many people, but its application to therapy has been very limited. The ways in which nutrition and the thyroid hormone can lower estrogen production just aren't being discussed in the books that recognize the role of estrogen dominance in the menopause.

Gradually, a few people are recognizing that progesterone can be used for other situations in which estrogen causes sickness. The role of estrogen in epilepsy, depression, circulatory disorders, and migraine is starting to be recognized, because of the immediate effects of supplemental progesterone. But estrogen's role in emphysema, asthma, liver and gall-bladder disease, diabetes, arthritis, strokes, movement disorders, memory problems, multiple organ failure, and a variety of inflammatory conditions is being neglected, for reasons that are largely ideological.

In pregnancy, menstrual disorders, and menopause, the situation makes it easy to think of the sex hormones, and the idea of balancing two of them seems plausible. Katharina Dalton popularized the idea that the premenstrual disorder could be diagnosed by finding a monthly rhythm in the symptoms, and treated by taking progesterone premenstrually. That was an extremely important contribution, because it gradually made doctors realize that the "syndrome" wasn't just a matter of monthly water retention, as the journals had characterized it.

But when the sickness doesn't have a clear monthly rhythm, or isn't associated with menopause, or isn't cured by supplemental progesterone, or occurs in a man or child, estrogen's role can easily be overlooked. If a problem is caused by stress, or x-rays, or aging, or a genetic mutation, some people think estrogen and progesterone are irrelevant.

This is because of a medical culture and ideology. As long as that culture defines the issues, very simple approaches to "insoluble" health problems are going to be ignored.

If we learn to see the problems in terms of a general disorder of energy metabolism, we can begin to solve them.

A. The Issues

Before genes were known to be made of DNA, some people spoke of the nucleus as if it were the "brain of the cell," although many experiments showed that idea to be very misleading.

100 years ago the doctrine of Weismannism explained the development, from a single cell, of organisms with many different kinds of cell, by saying that all of the genes were contained in the first cell, but that as the fertilized egg divided, the genes were distributed, divided up so that each tissue received only the genes that it needed for its specific structure and function.

While this doctrine was in force, the development of tumors, which often produce cells with some of the characteristics of other tissues, was neatly explained as the growth of a fragment that was "displaced" during the embryo's growth: "an embryonal rest." Dermoid tumors or pilonidal cysts are still usually explained as displaced embryonic tissue. Many other things, especially aneurisms (some aneurisms, e.g., "berry aneurisms," resemble tumors), that appear at any point in life are commonly described as "congenital," because of the great and lingering influence of Weismannism, which held that developmental potential existed only in the "germ line" cells. These ideas persist in the medical culture because of the uncritical nature of medical training.

The doctrine, the culture, of Weismannism is behind the desire to say that the nucleus, with its genes, ***controls*** the cell.

The people who like to think that the "genes control the cell" have built their more modern understanding of human and mammalian biology on ideas that were developed in the 1950s and 1960s for explaining the responses of bacteria to different kinds of food. In bacteria, there is no distinction between nucleus and cytoplasm, and their DNA isn't arranged in chromosomes. Their appropriate adjustments to changes in their environment were explained in terms of regulatory molecules that activate and inhibit specific

"The results strongly suggest the possibility that all mRNAs may be expressed in a single human cell, of both somatic and germ lineage." *Y. Kimoto, 1998*

genes. (As I have mentioned before, the work of John Cairns [Cairns and Foster, 1991] and others has shown that there is something fundamentally wrong with this idea, even for explaining bacterial physiology.)

These ideas were applied to explaining the more complex processes that regulate cells that contain a nucleus. The gene-***discarding*** details of Weismannism were dropped, in favor of a new doctrine, in which genes were bound up and inactivated, except when they were specifically activated according to the specific needs of a tissue.

Hormone receptors were seen as analogs of the regulatory molecules in bacteria. The receptors that the drug companies talk about are almost always understood in terms of the bacterial regulatory model, in which a protein binds to a drug or a signal substance, and then moves into the nucleus where it binds to specific genes. (In this scheme, the hormone is said to be "providing information" to the cell, regulating the "information in the genes.")

In neurology, receptors have been used to explain why all nerves don't respond in the same way to molecules such as adrenaline, acetylcholine, and dopamine. During development certain of their genes were activated, producing the receptors that allow them to respond only to certain substances.

The two kinds of receptor belonged to two different cultures--endocrinologists simply believed that nerves didn't have estrogen receptors, and neurologists believed that the relevant gene expression was taken care of before birth. Both of these cultures have turned out to be radically mistaken.

Because of the idea that activation of genes by receptors had to explain everything, estrogen was said to act only through its "receptor protein," and for decades most biologists simply denied that estrogen could have essentially instantaneous effects on cells, the way nerve transmitters do. As hundreds of "impossible" facts piled up, the scientific/medical establishment bent a little, and decided that there was another estrogen receptor, which would account for the immediate actions of estrogen. The alpha and beta estrogen receptors are now familiar entities, if we believe what is being said by many medical endocrinologists.

But estrogen does many things, and some of them clearly don't involve either the "alpha" or "beta" receptor proteins. Rather than making it easier to understand all of estrogen's effects, another "receptor" is just another distraction, making it easier to ignore some of the unexplained facts.

What began as a reductionist attempt to explain everything in terms of chance and mechanistic materialism, has resulted in an infinite tangle of assumptions and wild interpretations.

What, specifically, is wrong with the idea that a hormone binds to and activates a receptor protein which then activates certain genes?

First, it has been asserted for more than 30 years that this is the only way a hormone can work. A few years ago, the single estrogen receptor was supplemented by another receptor. In mice which have been mutated to lack these receptors, there are still responses to estrogen, and so a "receptor X" has been proposed. As long as a cell or organism can respond to something, it will be claimed that there is a receptor for it.

Second, the "classical hormone receptor" idea claims that the receptor/response system is highly specific, and is activated by a highly specific binding of the hormone to the receptor, and of the complex to the gene.

Third, the doctrine claims to be so important that other processes of regulation and differentiation of cells are forgotten or treated as if they were trivial.

The first objection is really an objection to the medieval way of thinking, in which every reaction has to be reified, turned into a concrete object. This attitude seems to be useful in getting funding.

The second false claim has been amply disproved--the range of things which can activate estrogen receptors is great, and the evidence that falsifies the claim has existed longer than the identity of the estrogen molecule has been known.

The third point will be settled by anyone who investigates the massive amount of research demonstrating that cell physiology and structure are thoroughly dependent on processes that occur after the genes have produced their product, messenger RNA. The stabilization and degradation of the RNA, and its rearrangement and splicing, are clearly very closely connected with the cell's nature and function.

There might turn out to be many interesting "repressors" and "activators" of specific genes, that conform to the standard bacterial model, but that hasn't been what the drug industry wants us to believe. They have an interest in selling the idea that hormones and drugs have a specific ability to "unlock" certain genes. Estrogen might no longer unlock the "femininity genes," but it is supposed to unlock the genes that protect the bones, heart, and brain. The "estrogen receptor" no longer has anything at all to do with femininity. It is found in every organ of both men and women. When a mutant mouse was produced that lacked an estrogen receptor, testicular edema was one of the most noticeable problems. (There might be reason to think this indicates an *increased* activity of estrogen in the absence of the receptor: See Sowerbutts, et al., 1986).

The conversion of estrogen, in the early 1960s, from something that "increased fertility" to something that prevents fertility, started a process that convinced the industry that they should concentrate their sales effort on women who are already infertile. That probably saved the industry from extinction, since the use of estrogen during pregnancy caused not only miscarriages, but also birth defects and cancer and other diseases in the children. But the present claims that estrogen activates specific genes that protect the aging tissues will eventually sound as foolish as the idea of "femininity genes" does now.

Without the receptor doctrine, the introduction of new drugs might require evidence of actual health benefits.

The facts of hormonal control of cell function are much more interesting than the simple receptor dogma.

B. Some Evidence

Within the last few years, a new technique (reverse transcriptase-polymer chain reaction) has made it possible to detect very small amounts of RNA, to show in a very clear way whether certain genes in a single cell are active.

Y. Kimoto has applied the test to several very different types of cell. Some genes involved in energy production and the basic maintenance systems are known to be active in all sorts of cells, but other genes, such as those that are responsible for the highly specialized functions of mature tissues, are believed to be inoperative in tissues with a different kind of specialization. He showed that all of the 25 types of RNA, for making very different kinds of protein, were present in each type of cell. ***"These findings strongly suggest that every cell can express every mRNA. Beneath the cell differentiation there may exist a DNA-->RNA basal constant flow...."***

If all of the organism's genes are always active in every cell, then the question is clearly "what really governs the cell's differentiation, and the varying expression of the genes' protein products?"

When a cell doesn't need a particular kind of RNA, it is degraded almost instantly. When it is pressured to adapt in a certain direction, the RNA for making the adaptive proteins becomes very stable, and accumulates.

A similar process occurs with proteins, degrading them quickly, or protecting them. In many enzymes, a vitamin or other coenzyme binds to the protein and stabilizes it.

If the enzymic activity is changed in the presence of a hormone, many people have assumed that new proteins with different functions were produced by activation of genes, but in many cases, hormones (like vitamins) directly alter the functions of enzymes.

In the 1960s, Engel and his collaborators showed that estrogen binds to several enzymes, and that the association of estrogen with the enzyme alters the cell's chemistry, including the balance between oxidation and reduction. These enzymes could very properly be called "estrogen receptors," because they mediate the cell's response to estrogen. But the general atmosphere was such that only receptors which moved into the nucleus and bound to a gene could be accepted. Everything had to be explained by the prestigious bacterial model.

Nevertheless, in the 1960s and earlier there were other people who could demonstrate that basic changes in the cell's chemistry altered the expression of genes. C.D. Cone, Jr., showed that osmotic forces and the cell's surface electrical potential, which he manipulated by adjusting the ratio of sodium to potassium, could powerfully activate the genes. He demonstrated that even the nuclei of brain cells could be stimulated to undergo mitosis, duplicating their DNA as a result of a simple change of the salt balance.

Around 1985, stress (high temperature, or deprivation of oxygen or glucose, for example) was found to alter gene expression in a systematic way. **It turned out that estrogen activates these same "stress proteins."**

This was particularly interesting, since many years earlier it was demonstrated that many kinds of stress imitated the function of estrogen. Suffocation or x-ray exposure (of the brain, or ovary, or any part of the body) would trigger the lordosis reaction, for example. More recently, it has been noticed that a moderate x-ray exposure of the brain can bring on premature puberty in girls. And irradiation (x-rays, gamma rays, or ultraviolet rays) synergizes in other ways with estrogen, for example in causing cancer.

The estrogen receptor, even without any estrogen, will still move into the nucleus and bind to the genes, under the stress of oxygen deprivation. This is consistent with the idea that estrogen is doing something to the cell that resembles the changes produced by the other stressors. Under more objective circumstances, the "estrogen receptor" might have been identified as just another of the components in a stress response.

Heat shock can increase the number of estrogen receptors (Marin, et al., 2001). Estrogen, too, generally increases the quantity of the estrogen receptor protein.

Testosterone, thyroid, cortisone are known to stabilize certain RNAs, causing the expression of gene products without necessarily doing anything directly to the gene. The overwhelming emphasis in research now seems to be on the factors that regulate the stability of RNA, rather than on the simpler bacterial model of gene activation.

In 1996, many people spoke of the original estrogen receptor as if it moved "from the membrane" through the cytoplasm to the nucleus, because of a habit of thinking of the cell surface as a "membranous barrier." But the protein that they identified as their estrogen receptor was in the cytoplasm.

For more than 30 years, people had been noticing that estrogen had many effects that were practically instantaneous, for example causing cells to take up water and alter their electrical behavor. Cone's work demonstrated that the cell's water content and electrical behavior could activate the nucleus, so I didn't see the need for having separate explanations for regulating water, ions, electrical potentials, and genetic expression.

But the Other Major Dogma of cell biology has been that "the plasma membrane" regulates everything. When people heard about estrogen's or progesterone's or the thyroid hormone's instantaneous actions, they thought it must be a membrane-controlled response.

V.D. Ramirez and his collaborators began talking about the reality of a second estrogen receptor, the beta receptor, or membrane-associated receptor. (The original "gene activating receptor" has now become the alpha receptor.)

Their definition of "membrane" was very standard: First you homogenize the tissue, and then centrifuge it, and certain layers of the sludge are called membranes. That's because of the tradition in which membranes served to enclose the "watery" cytoplasm, so naturally they were the part that wasn't watery, i.e., they were the insoluble lump left after homogenization and centrifugation.

But they identified several proteins that estrogen stuck to: **ATPase (regulating energy and salt and water), and GAPDH, the rate controlling enzyme of glycolysis. Estrogen activates this enzyme, and physiologically estrogen activates the glycolytic pathway, increasing the production of lactic acid as it shifts metabolism away from mitochondrial oxidation, lowering the cell's ATP production, and shifts the use of oxygen functions, such as producing nitric oxide, the free radical which is a common mediator for all the harmful forms of radiation, and for oxygen deprivation.**

This particular enzyme interests me, because of its function in controlling glycolysis, but also because it is inactivated by cold, along with other important enzymes involved in the estrogen reaction. In 1971 I proposed that estrogen activated this enzyme by altering the "structural temperature" of the cell water, something which paralleled C.D. Cone, Jr.'s sodium/electrical effects, that is, it would be a holistic shift in the way the insoluble ("membrane") proteins behaved, making them more insoluble or hydrophobic.

But Ramirez's group, like Engel's, was suggesting that the binding of estrogen to the enzymes, changing their activity, was the regulatory principle, which doesn't make too much difference, since the various interpretations end up causing the same metabolic shifts, toward the metabolism of stress, or cancer, or estrogen dominance. The shift of metabolism toward lactic acid production and lower energy production will also cause some holistic changes, such as changing the redox balance, possibly increasing the pH, and lowering the energy charge. However, I think a change in the cell's hydrophobicity or structural temperature would also make coherent changes in the stability of RNA as well as of proteins.

The activation of the other enzyme, ATPase, in Ramirez's experiments, is even more supportive of the idea that estrogen is modifying the cell water, lowering its order the way increased temperature would. In the mitochondrion, the enzyme that synthesizes ATP (ATP synthetase) will also destroy ATP, if conditions are changed.

The three main conditions that cause the enzyme to destroy ATP are prolonged standing after separating the mitochondria from the cells, freezing the mitochondria and then slowly thawing them (messing them up more thoroughly than when they are rapidly thawed), and treating them with estrogen.

Destroying the cell's ATP at a high rate is an important factor in forcing the cell to get its energy from glycolysis, producing lactic acid.

All of the stages involved in the development of cancer are promoted by estrogen. For example, the local acidification produced by lactic acid production promotes invasiveness, by activating proteolytic enzymes.

The mere presence of lactic acid in the blood displaces carbon dioxide, with many harmful consquences (all of which are seen in the estrogen dominant state). Carbon dioxide is in effect our basic protection against free radical damage. (Boljevic, et al., 1996.) Carbon dioxide is generally thought to be a major factor in regulating the balance of water in the body. For example, hyperventilation increases capillary leakiness, and causes fluid to leak out into the tissues. Estrogen decreases carbon dioxide by causing hyperventilation and increased lactic acid production. **Estrogen systemically increases capillary leakiness.** (Cho, et al., 1999; Ziylan, et al., 1990; Reid, et al., 1983; Merlen, 1982.) **The capillary leakiness is corrected by progesterone.** (Lagrue, et al., 1983.)

The idea that estrogen increases the structural temperature of cell water, even while the real temperature might be decreasing, would be consistent with the fact that the "heat shock" or stress proteins are expressed under estrogen's influence. And when, under the influence of estrogen or the unsaturated fatty acids, cells take up more water, they also take up a little sodium. This reduces the organizing influence of the cell's proteins on the water, and this is what increases its structural temperature. When the nervous system, responding to estrogen, "sets the thermostate lower," there is a slight restoration of the cell's water and protein interactions, but metabolic processes are slowed at the lower temperature.

Estrogen, like radiation and oxygen deprivation, increases formation of the nitric oxide (NO) free radical, which has so many harmful effects, ranging from damaging DNA to poisoning mitochondria. One of the consequences of increasing NO formation (and estrogen) is the activation of an enzyme (heme oxygenase) which produces carbon monoxide, in the process of breaking down the heme molecule (which is needed for respiratory enzymes, among other essential functions). In previous newsletters I have discussed the reasons for thinking that endogenously produced carbon monoxide could explain the gradual development of cancer, since it stabilizes cells in the primitive anti-respiratory condition.

Any injury that an organism can survive is likely to activate the defensive systems, increasing the organism's ability to survive a subsequent stress (e.g., Meerson, et al., 1991), and this seems to explain why estrogen treatment sometimes has a protective effect. In a healthy menstrual cycle, estrogen's dominance is present for just a few hours, and this short stimulus serves to stimulate compensatory production of progesterone. Ever since Lipshutz's experiments in the 1940s, it has been known that it is the prolonged, uninterrupted action of estrogen that is profoundly harmful, not the brief cyclical exposures.

It's the prolonged shock-like state that contributes to the degenerative diseases, which typically begin with a sort of diabetes, an inability to use glucose for energy because of the accumulation of too much of the wrong kind of fat.

C. Protective Measures

The avoidance of stress is the basic principle for preventing the development of the estrogen-dominant state. Since darkness is itself a stress, generally increased exposure to strong light that is rich in the long-wave part of the spectrum, yellow to red, is protective, since these frequencies restore enzymes damaged by stress. Avoiding ionizing radiation whenever possible is very important, and this includes especially medical/dental x-rays, which are almost always unnecessary.

The polyunsaturated fats, toxic heavy metals, and inappropriate amounts of certain amino acids, such as tryptophan, cysteine, leucine, and

glutamate, increase our sensitivity to stress of all sorts, including radiation, and so should be avoided as far as possible. Coconut oil or palm kernel oil (which is even more saturated than coconut oil, with a generous supply of the short fatty acids) should be used regularly, since it isn't possible to avoid the toxic unsaturated fats entirely. (Generally, starchy food should be avoided, for several reasons: Persorption, obesity, and the nature of the foods that contain them.)

Many drugs that are currently popular decrease stress resistance. A few drugs are protective in the short term, but are toxic if used for a long time. Aspirin protects against some of the worst stressors, including the polyunsaturated fats, so despite its mild toxicity, long term studies usually show that it decreases sickness and mortality. Antibiotics, though they are toxic in themselves, also have powerful antistress effects.

In stress, magnesium and sodium are lost rapidly, so the diet should contain foods such as fruits and meats that contain significant amounts of magnesium. Added sodium helps to spare magnesium.

Occasional use of liver, to assure a generous supply of vitamins and trace minerals, is safer than using chemical supplements. Niacin and thiamine help to correct some of the metabolic distortions created by stress or estrogen.

The specifically antiestrogenic hormones, thyroid (especially T3), pregnenolone, and progesterone, can compensate to some extent for exposure to any of the stressors, including ionizing radiation.

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Ray Peat's Newsletter

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Growth hormone: Hormone of Stress, Aging, & Death?

The name "growth hormone" is misleading; stress produces somatic growth, in a process called "hormesis." Exercise produces muscle edema, to a degree similar to that produced by GH; edema stimulates growth, but GH effect isn't limited to bone and muscle.

Identity of GH: Molecular ambiguity, complex modifications change one substance into many; its evolution suggests a role in water regulation. Doctrine of a "specific molecule" and "specific receptor" and specific effects is a myth.

The osmoregulatory problem--keeping water under control--is centrally involved in stress.

In mammals, the kidneys and bowel are the main regulators of water balance.

GH is a stress hormone. Its effects can be produced osmotically, for example inducing milk production and cartilage growth, by osmotic (dilution) shock.

Estrogen produces increased GH, and increases its production in stress.

Nitric oxide is a pro-aging free radical induced by estrogen, releasing GH; all three produce edema.

Behind edema, hypoxia, hypocarbia; free fatty acids, diabetes, vascular leakiness, degenerative kidney changes, connective tissue changes, thickened basement membrane, retinal degeneration. The same changes occur in aging: increased permeability; kidney disease, connective tissue changes.

The absence of GH protects kidneys against degeneration. Osteoarthritis, a characteristic aging condition, is caused by estrogen and GH.

Some studies found that heart failure and bone repair aren't improved by GH; GH is very high during heart failure, in which edema contributes to the problem; carpal tunnel syndrome, myalgia, tumor growth, gynecomastia, and many other problems have been produced by GH treatments.

Recently I heard Robert Sapolsky interviewed, and he was describing the changes that prepare the body for short-term stress. He said the energy-mobilizing hormones, adrenalin and cortisol, increase, while the hormones that don't contribute to meeting the immediate problem, including the sex hormones and growth hormone, are suppressed, to save energy; growth and reproductive processes can be suspended for the few minutes of acute stress, to make the body more able to meet its acute needs. He reiterated: Growth hormone is suppressed by stress.

Sapolsky has done very interesting work on the suppression of testosterone by stress, and on the way in which brain cells are killed by prolonged exposure to glucocorticoids. He showed that if extra glucose is supplied, the brain cells can survive their exposure to cortisol. In the body, adrenalin and the glucocorticoids increase the availability of glucose.

In the radio interview, he didn't have time for much detail, but it seemed to me that he wasn't talking about the same growth hormone that I have been reading about, and trying to understand, for years. Since people have asked me to write about the current anti-aging uses of GH, and its use in the dairy industry, Sapolsky's statements made me decide to think about some of the issues around the hormone.*

Bovine Growth Hormone is used to make cows give more milk.

Human Growth Hormone is supposed to make men lean and muscular, not to increase their milk production.

The "growth hormone" was named long before it was actually found, and the substance with that name turns out to be involved in many

processes other than growth. It is being given to cows to make them produce more milk, and it is being given to people with the purpose of making them lean and muscular, and with the hope of building stronger bones.

It isn't surprising that the Growth Hormone helps breasts develop and promotes milk production, since it is very similar to prolactin. GH and prolactin are members of a family of proteins that have diverged from each other in evolution, but they still have many overlapping effects.

When GH is treated as a drug, it is supposed to have a discrete identity, based on the sequence of its amino acids. But the natural hormone (disregarding the existence of a variety of closely related peptide with slightly different amino acid composition) varies with time, being chemically modified even before it is secreted. For example, its acidic amino acids may be methylated, and its lysine groups may combine with sugars or carbon dioxide. **The *history* of the protein in the body determines its exact structure, and therefore its biological effects.**

Male animals secrete GH in pulses, but females secrete it more steadily. This pattern of secretion "masculinizes" or "feminizes" the liver (and other organs), determining the pattern of enzyme activity. It would be possible (though very difficult) to arrange a system for delivering doses in a pulsed, intermittent manner. In cows, this apparently isn't necessary, since the purpose of the growth hormone is presumably to "feminize" the milk-producing system. But the normal pattern of secretion is much more complex than simply being "pulsed" or "continuous," since it, like prolactin secretion, is responsive to changes in thyroid, estrogen, diet, stress, and many other factors.

**If Sapolsky had been talking about just mice and rats, his statement would have been generally accurate. Adrenaline stimulates rat pituitary cells to secrete GH, and since both increase the amount of free circulating fatty acids, it could be that rats' GH is suppressed by a fatty acid excess.*

For example, hormones in this family are, as far back in evolution as they have been studied, involved in the regulation of water and minerals. It is well established that increased water (hypotonicity) stimulates prolactin, and increased sodium inhibits its secretion. Growth hormone is also closely involved with the regulation of water and salts.

One of the best known metabolic effects of GH is that, like adrenalin, it mobilizes fatty acids from storage. GH is known to antagonize insulin, and one of the ways it does this is simply by the ability of increased free fatty acids to block the oxidation of glucose. At puberty, the increased GH creates a mild degree of diabetes-like insulin resistance, which tends to increase progressively with age.

In his book, *Why Zebras Don't Get Ulcers,* Sapolsky acknowledges some situations in which GH is increased by stress in humans, but I think he misses the real ways in which it operates in stress. One of the interesting features of cortisol, which Sapolsky showed killed brain cells by making them unable to use glucose efficiently, is that it makes cells take up unsaturated fatty acids more easily, interfering with their energy production. Since growth hormone also has this kind of "diatebetogenic" action, it might be desirable to suppress its secretion during stress, **but in fact, there are several kinds of stress that clearly increase its secretion, and in animals as different as fish, frogs, cows, and people it can be seen to play roles in water and salt regulation, growth and development, stress, and starvation.**

Heat, hypoglycemia, running, and some types of shock are known to stimulate growth hormone secretion, sometimes to levels ten or twenty times higher than normal. (Two kinds of stress that usually don't increase GH are cold and stimulus-deprivation.) I consider the growth hormone to be, almost as much as prolactin, a stress-inducible hormone. That's why I reasoned that, if an endocrinologist as good as Sapolsky can misunderstand GH to that degree, the public is even more likely to misunderstand the nature of the material, and to believe that it somehow acts *just on muscle, fat, and bones.*

And the normally functioning pituitary appears to be unnecessary to grow to normal height. (Kageyama, et al., 1998.)

W. D. Denckla discovered that the pituitary hormones are in some way able to accelerate the process of aging. They block the actions of thyroid hormone, decreasing the ability to consume oxygen and produce energy. The diabetes-like state that sets in at puberty involves the relative inability to metabolize glucose, which is an oxygen-efficient energy source, and a shift to fat oxidation, in which more free radicals are produced, and in which mitochondrial function is depressed. Diabetics, even though it is supposedly an inability of their cells to absorb glucose that defines their disease, habitually ***waste glucose, producing lactic acid*** even when they aren't "stressed" or exerting themselves enough to account for this seemingly anaerobic metabolism. It was noticing phenomena of this sort, occurring in a great variety of animal species, in different phyla, that led Denckla to search for what he called DECO (decreasing consumption of oxygen) or "the death hormone." (Vladimir Dilman noticed a similar cluster of events, but he consistently interpreted everything in terms of a great genetic program, and he offered no solution beyond a mechanistic treatment of the symptoms.)

Simply increasing the amount of free fatty acids in the blood will act like DECO or "the death hormone," but growth hormone has more specific metabolic effects than simply increasing our cells' exposure to fatty acids. The hormone creates a bias toward oxidizing of the most unsaturated fatty acids (Clejan and Schulz), in a process that appears to specifically waste energy.

Growth hormone plays an important role in puberty, influencing ovarian function, for example.

Removing animals' pituitaries, Denckla found that their aging was drastically slowed. He tried to isolate the death hormone from pituitary extracts. He concluded that it wasn't prolactin, although prolactin had some of its properties. In the last publication of his that I know of on that subject, he reported that he was unable to isolate the death hormone, but that it was "in the prolactin fraction." Since rats have at least 14 different peptides in their prolactin family, not counting the multitude of modifications that can occur depending on the exact conditions of secretion, it isn't surprising that isolating a single factor with exactly the properties of the chronically functioning aging pituitary hasn't been successful.

Denckla's experiments are reminiscent of many others that have identified changes in pituitary function as driving forces in aging and degenerative diseases.

Menopause, for example, is the result of overactivity of the pituitary gonatropins, resulting from the cumulatively toxic effects of estrogen in the hypothalamus.

A. V. Everitt, in his book on the hypothalamus and pituitary in aging, reported on studies in which **estrogen caused connective tissues to lose their elasticity, and in which progesterone seemed to be an antiestrogenic longevity factor.** Later, he did a series of experiments that were very similar to Denckla's, in which removal of the pituitary slowed the aging process. Several of his experiments strongly pointed to the prolactin-growth hormone family as the aging factors. Removal of the pituitary caused retardation of aging similar to food restriction. These pituitary hormones, especially prolactin, are very responsive to food intake, and the growth hormone is involved in the connective tissue and kidney changes that occur in diabetes and aging.

A mutant dwarf mouse, called "little," has only 5% to 10% as much growth hormone as normal mice, and it has an abnormally long lifespan.

Many experiments show that prolactin and estrogen have synergistic effects in causing tissue degeneration, including cancerization, and that their effects tend to operate with fewer protective restraining influences in old age. Estrogen stimulates both prolactin and growth hormone secretion. Thirty years ago, people were warning that estrogen contraceptives might produce diabetes, because they caused chronic elevation of growth hormone and free fatty acids.

Since estrogen causes a slight tendency to retain water while losing sodium, producing hypotonic body fluids, and since hypotonicity is a sufficient stimulus to cause prolactin secretion, I

have proposed that it is estrogen's effect on the body fluids which causes it to stimulate prolactin. In pregnancy, the fetus is exposed to fluids more hypotonic than can be accounted for by estrogen and prolactin alone; since GH lowers the salt concentration of fish when they enter the ocean from freshwater, it seems to be a candidate for this effect in pregnancy.

Growth itself is an intrinsic property of all cells, but the growth hormone does have its greatest influence on certain tissues, especially cartilage. Gigantism and acromegaly were what originally made people interested in looking for a growth hormone, and these are characterized by continued, exaggerated enlargement of bones and cartilage. In old age, cartilaginous structures such as the bones and ears keep enlarging. The fact that simply diluting the culture medium is sufficient to stimulate the growth of cartilage suggests that the growth hormone might be acting by its effects on water metabolism. **In fish which enter fresh water from the ocean, pituitary hormones of this family help them to balance salts in this new environment, but in the process, they develop osteoporosis and skeletal deformity, of the sort that occur more gradually in other animals with aging.**

Growth hormone clearly causes edema, and this is probably involved in the pathological processes that it can produce. The expansion of extracellular water has been reported, but others have concluded that the increased weight of muscles following GH treatment must be the result of "growth," **"because microscopic examination didn't show edema."** Statements of that sort give incompetence a bad name, because any student of biology or biochemistry has to know, before he does almost any experiment, that the way to determine the water content of a tissue is to compare the wet weight to the weight after thorough drying. Looking for water under a microscope is the sort of thing they do at drug companies to pretend that they have done something.

Estrogen, growth hormone, and nitric oxide, which tend to work as a system, along with free fatty acids, all increase the permeability of blood vessels. The leaking of albumin into the urine, which is characteristic of diabetes, is promoted by GH. In diabetes and GH treatment, the basement membrane, the jelly-like material that forms a foundation for capillary cells, is thickened. The reason for this isn't known, but it could be a compensatory"anti-leak" response tending to reduce the leakage of proteins and fats.

Besides being involved in kidney degeneration, vascular leakiness contributes to brain edema, and probably contributes to the "autoimmune" diseases.

Whatever the exact mechanism may be, it is clearly established that GH contributes to kidney degereration, **and the lack of GH, even the removal of the pituitary, is protective against kidney degeneration.**

Denckla's and Everitt's experiments can be interpreted much more clearly now that GH's essential contribution to kidney degeneration is known. Growth Hormone may not be precisely the Death Hormone that Denckla was looking for, but it is very close to it. **Anti-thyroid effects have been seen, and possibly even anti-growth effects during gestation, and in kidney disease. In newborns, high GH is associated with smaller size and slower growth;** in one study, this was associated wtith rapid breathing, presumably hyperventilation which is associated with stress. The shift to the diabetes-like fatty acid oxidation would be expected to inhibit respiration, and the chronic elevation of serum free fatty acids will have a generalized antithyroid effect. **Under the influence of GH, the proportion of unsaturated fatty acids is increased, as occurs under the influence of estrogen.**

Growth hormone blocks gonadotropin-stimulated progesterone production, and this could also affect thyroid and respiratory metabolism.

The increase of GH during sleep might seem to be utterly incompatible with the idea that it is a stress hormone, but in fact the other stress hormones, adrenalin, cortisol, and prolactin also tend to increase during night-time sleep. Thyroid function and progesterone function decrease at night. As I have argued previously darkness is one of our major stressors. Considering GH's tendency to cause edema, tissue swelling, it could

play a role in the nocturnal increase of the viscosity of blood, as the volume of blood is decreased by the leakage of fluid into the tissues. Another process with potentially deadly results that increase withaging and stress, is the passage of bacteria from the intestine into the blood stream; this process is increased under the influence of GH.

Acute, short term studies definitely show growth hormone to be a stress hormone with some destabilizing effects. Over a lifetime, it is possible that such things as chronically increased levels of unsaturated fatty acids in the blood, and increased leakiness of the blood vessels, could cumulatively produce the effects that Denckla ascribed to the Death Hormone.

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Ray Peat's Newsletter

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THE ORIGINAL ARGUMENT:

Cancer is the result of ordinary physiological processes which become autonomous because of regulatory weaknesses in the organism.

Respiration is essential for the maintenance of the higher forms of life, and it is a respiratory defect, on both the cellular and the organismic levels, which allows cancer to persist and develop.

The heme group, because it serves many respiratory functions--hemoglobin, mitochondrial respiratory enzymes, steroid synthesizing enzymes, formation of thyroid hormone, detoxifying enzymes--is regulated in relatively primitive ways within each cell, and in more complex ways at higher organismic levels.

When the cell needs more respiratory energy, some fuel is diverted into the production of porphyrin, which is then turned into heme, which would normally provide for the efficient production of energy and protective factors.

When the efficient energy-producing systems are blocked, by injury, oxygen deficiency, toxins, or by the lack of one or more essential nutritional factors, heme production is activated.

Excess heme is destroyed by the enzyme heme oxygenase, which converts heme into biliverdin and carbon monoxide. Both of these factors have effects on the cell which are characteristic of cancer.

Estrogen, radiation, chemical carcinogens, and other forms of stress, activate the heme oxygenase enzyme.

Estrogen causes both porphyria and jaundice and is associated with increased formation of carbon monoxide. It inhibits many types of liver function, including detoxification.

The production of carbon monoxide by cancer cells can account for cancer's self-sustaining, "hereditary," property, without invoking genetic mutations which are now known to be consequences, rather than causes of cancer.

The production of carbon monoxide and biliverdin can account for many of the structural and biochemical abnormalities of cancer cells, and for their induction of abnormalities in adjacent cells.

"Genetic" theories of cancer have now reached a dead end, and the epigenetic, developmental-physiological approach remains as the only plausible description of cancer.

Carbon monoxide, estrogen, and the medical cancer cult

Previously when I wrote about the role of endogenously formed carbon monoxide in cancer, I probably didn't say enough about the way the idea fits into our cultural context. If an idea is very different from the existing cultural matrix, it's probably useful to consider it in its historical setting, and to contrast its theoretic models and implications with conventional models and practices, besides looking at some of the evidence that could confirm it.

During Otto Warburg's lifetime, many people working on the cancer problem were sufficiently aware of his work (because of his Nobel prize) that they occasionally mentioned it dismissively. Now, very few people even know about his cancer research and his conclusion that the prime cause of cancer is a cellular respiratory defect. For about 30 years, the dunces were in confederacy against him, then they forgot what it was about his work that had bothered them.

Dean Burk, who was head of the cell biochemistry laboratory at the NIH for many years, was the only well known American who defended Warburg's interpretation of cancer, and now that they both have died, cancer researchers just don't feel the need to mention Warburg's work at all.

In practice, science isn't a matter of a rational evaluation of evidence, but rather it's a matter of power, funding, and propaganda. In our culture, the understanding of cancer has been guided since the late 1940s by the propaganda of the American Cancer Society, supported by the corporate cancer industry and, especially since Nixon's War on Cancer began in 1971, by government funding.

Warburg's work showed that anything which causes tissue atrophy contributes to the development of cancer, and that interference with the

cells' ability to use oxygen for energy production was the essential factor in cancer. Warburg was exploring this simple deterministic biochemical, physiological and developmental process in Germany just as quantum mechanics was destroying classical physics and Nazism was enforcing the dogma of genetic determinism and eugenics. The revision of Darwinism taking place at this time turned the doctrines of random mutation of genes and selection of "superior genes" into the essential core of biology and medicine.

The same concepts were used to describe socially undesirable people (people whose genes had "degenerated") and the biologically undesirable cells of cancer.

There were reasons for commerce and government to favor a theory of cancer in which a mysteriously random process turned a normal cell into a deadly alien cell that multiplied wildly and invaded and destroyed surrounding healthy tissues. One reason was that causes of cancer, such as soot, radiation, and estrogen, would become very unpopular if the public recognized the causal pathways between them and cancer, and polluters could be sued or accused of murder, and drug companies would lose the chance to market all of their infinitely profitable estrogens.

And the idea of a mysteriously mutated cancer cell ruled out the idea of any therapy that would cause the cancer to regress or disappear in a physiological manner that didn't harm any other part of the body. The already established treatments of surgical removal, destruction by radiation, or destruction by cytotoxic chemicals were justified by the doctrine that the tumor, the clone of cells produced from the mutant cell, was irreversibly committed to its condition.

The scientific foundation for that view of cancer has really been destroyed over the last fifty years, but it is rare to encounter a physician or professor of medicine who is aware of that. Even the majority of biology professors haven't realized the decisive nature of the evidence against it, because most of them don't read outside their own specialty.

Oncology (which should mean the study of tumors) is really a medical religion, filled with rituals and incantation-like use of language. Despite the abundant evidence that access to medical diagnosis and treatment doesn't improve health, most people are mysteriously bound to the "health care system." Hotels don't have 13th floors, many people don't like it when a black cat crosses their path, or they knock on wood at odd moments in a conversation, even though they aren't superstitious. The culture influences behavior, just by being there. When your friends recite their version of the medical incantations, and your doctor repeats them while wearing a white jacket and expensive shoes, it seems only decent to go along with the system. Even if patients would like to question their doctors' assumptions, they can't do it successfully within the medical culture, and few people are willing to take a hostile stance toward a system that monopolizes many useful drugs.

The mutant cell/clonal theory of cancer reduces the issue to a matter of choosing the best way to kill the patient's tumor without killing the patient. Very slowly, the practice of using a single modality against each type of tumor is being replaced by trials using several substances at the same time, or sequentially, and oncologists now sometimes magnanimously allow their patients to take vitamins as well as psychotherapy, though many have feared that the vitamins might interfere with their work.

Outside the medical world of oncogenes and mutations, the understanding of cancer as a disorganization of metabolism and regulatory processes is advancing.

Johanes Muller argued in 1840 that cancer might originate at the level of tissues, rather than in the nature of the individual cells making up the tissue. More recently, David Smithers described cancer as a problem of organization, analogous to a traffic jam, which can disrupt the system even while no particular vehicle is defective. Generally, this view speaks of a "cancer field," in which whole regions of an organ show different degrees of a precancerous or cancerous state.

The "precancerous" condition of some of the cells within the cancer field can be shown to be induced by something emitted by seriously injured cells nearby. In radiation research, these effects are now described as the "bystander effect," in which unirradiated cells that are exposed to

radiation-damaged cells will develop some of the physiological features of the irradiated cells. Some kind of "toxic signal" has been released from an injured cell, inducing a similar injury in the healthy cells.

Irradiated tissues respond with most of the features that are involved in general systemic stress--lipid peroxidation, free radicals, increased glycolysis, and a shift of metabolism toward production of the "emergency" factors that increase resistance in the short term. Other kinds of injury--overstimulation or energy deprivation, for example--cause cells to produce the same sorts of signals that affect surrounding cells. The extracellular matrix in which cells are embedded transmits these signals, partly by undergoing its own transformation into a differently structured matrix.

Systemic metabolic problems make local problems worse, and if a local injury is serious, it can cause the liver to produce stress-related proteins called "acute phase proteins," including fibrinogen and serum amyloids A and P, C-reactive protein, and other inflammation-related proteins. These proteins are a primitive sort of immune system, that can directly bind to some harmful substances. Endotoxin absorbed from bowel bacteria is probably the commonest reason for increased production of these proteins. The acute phase proteins contribute to the development of tumors in various ways. For example fibrinogen degradation products are pro-inflammatory. Although these are called acute phase proteins, they sometimes might better be called chronic inflammation proteins, since they are associated with diabetes, cancer, and heart disease.

The systemic principle of cancer involves the same inflammatory mechanisms that are involved in circulatory diseases, strokes, multiple sclerosis, multiple organ failure, etc. An inflammatory process that isn't controlled causes blood vessels to leak, and the process of disposing of the leaked materials, if the leakage is extensive, leads to reactions of the whole organism; usually, the signals reaching the higher levels of organization evoke a stress-limiting response, and stability is restored, but if conditions aren't just right, the stress-induced damage accumulates. With repeated injury, and with chronic accumulation of polyunsaturated fats, fibrosis, atrophy and inflammation increase, and the energetic intensity of corrective responses decreases.

The first reaction to serious injury, challenge or deprivation is to prepare for growth and cell division. The simple production of lactic acid when oxygen supply isn't adequate causes blood vessels to dilate. Energy production becomes inefficient; the fatty acid synthesizing enzyme system is activated, even when large amounts of fat are being made available by lipolysis under the influence of stress. In proportion to the challenge, capillaries become more permeable, and cells may begin to enter the tissues from the bloodstream, along with water and nutrients. A surge of cell division allows renewal of damaged cells. If the inflammation persists, new capillaries grow, and larger vessels develop. Some of the immigrant cells may eat themselves to death removing debris, but others remain as colonists. Every inflammation is an incipient neoplasm. An organ such as the intestine, the liver, ovary, or thymus gland, is always in flux, renewing its cells, but when that renewal is disordered, the functions of the organ change, such that we speak of a neoplasm, a new growth, which in a sense is a new organ. It has been suggested (Zajicek) that the neoplastic organ has an adaptive, survival value, producing one or more substances that the body lacks.

Zajicek supports his idea with careful analysis of cancer statistics, and points out that it's very common for the removal of a large tumor to be followed quickly by the appearance of myriad small tumors. He thinks it would be better to leave the original tumor in place. His orientation is in the tradition of "chalone" research, in which every tissue stops growing at the proper time because it emits a substance which specifically inhibits its own growth. Over the last 50 years the idea has been confirmed by many experiments, but it hasn't made any impression on the cancer industry. Stating the idea in very broad terms, we might say that aging or stress causes atrophic processes including "sarcopenia" and "osteopenia," the reduction of the mass of various tissues below the proper level, and that tumors are the result of an uneven attempt to restore the proper mass of tissue.

I think Zajicek's idea would be more acceptable if it were stated in more general terms, without denying the possible role of chalones, or something like chalones that tends to protect the body or suppress tumors. Using Le Chatelier's principle,* that a system adjusts to disturbance in a way that reduces the disturbance, we could say that one function of a tumor might be to dispose of something that has disturbed homeostasis.

For example, insulin resistance produces an inability to oxidize glucose, and is associated with chronic hyperglycemia, or "type 2 diabetes." Diabetes of that type is associated with a high risk of cancer (e.g., Yam, et al., 1996). V.S. Shapot's decades of research led him to describe a tumor as a glucose scavenger (1979). When the system is disturbed by chronic hyperglycemia and an inability to use glucose, a sort of equilibrium will be restored by the production of a tumor that pumps glucose out of the system. Although tumors consume sugar and release lactic acid, they aren't really living on the sugar, they are doing something very odd: They convert a large amount of glucose into fat, and then oxidize the fat. The enzyme system, fatty acid synthase (FAS), is an effective way to dispose of glucose, because of its energetic inefficiency.

Another way to look at Zajicek's idea is to recognize that the main cause of insulin resistance is the dietary consumption of (both omega -6 and omega -3) polyunsaturated fatty acid, and that the fats produced by the FAS in tumor cells are mainly saturated fatty acids, with some of the antiinflammatory omega -9 series. In this case, Zajicek's suggestion that the tumor is producing something the body needs would be literally correct.

The same "epigenetic" processes that create our organs, under new conditions can create tumors. The doctrine of genetic determinism has almost reversed the basic meaning of "epigenetic," since developmental biologists talk as if developing organs were all programmed in the genome, and that they were created as if from a blueprint contained in the genes. During ordinary development, we think of epigenesis as a process that creates an organism in a certain environment, and we recognize that even the protected intrauterine environment allows great individuality of development, influenced by slight differences in conditions of nutrition, hormones, temperature, etc., during an individual's development. Epigenesis accounts for a lot of normal variation in traits--size of brain and other organs, rate of maturation, degree of pigmentation, etc.--and for many developmental defects. Epigenesis is an even more important concept for understanding tumors, despite the fact that so much money has been invested in explaining tumors according to oncogenes and other ideological inventions of the genetic determinists. Even oncogenes' expression is environmentally determined.

The normal cyclic function of the ovaries is a model for the potentially creative role of an inflammation-like stress. Every month (in a rhythm influenced by many cues), a productive crisis comes to a focus in the ovary, with the formation of estrogen, prostaglandins, carbon monoxide, and other signal substances, causing rapid changes both locally and systemically, with water, hormones, and nutrients gathering around the ovum (as well as in other parts of the body, such as the feet). Then as the follicle ruptures with the release of an ovum, the excitatory, inflammation-like state is resolved, with a massive increase in the production of the antiinflammatory, antistress substance, progesterone, leading to the suppression of the excitatory substances. **These monthly processes are developmental, they are part of the epigenetic development of the organ.**

Most, if not all, of the substances involved in ovarian physiology are involved in the diseases of stress and degeneration, which progress in proportion to the inability to produce the resolution of inflammation and restoration of the stable condition. The ovary is a major source of estrogen, which can produce the excited, activated, inflammatory and proliferative state in any tissue of the body, though it acts mainly on the uterus, breasts, and pituitary. But the ovary is also, in response, able to produce massive amounts of the protective progesterone, which interrupts the inflammatory effects of estrogen on the various tissues and organs, largely by suppressing the proteins that hold estrogen within cells (especially the "estrogen receptor"), but also by changing the activities of many enzymes away from the

estrogen-controlled, inefficient pattern. **The developmental actions of the ovary cause continuing epigenetic processes in other organs, causing noticeable changes in their structure every month.**

The ovary plays a specialized coordinating role in preparing the whole body for pregnancy, but most of its regulatory features can be seen in a diminished form in other organs, and in any tissue that is unable to completely resolve a crisis of inflammation. Considering ovarian processes and structures in detail will offer some insights into the processes that occur elsewhere during inflammation and tumefaction.

One of the rules of classical mechanistic endocrinology was that a hormone doesn't act on the organ that produces it, and acts only on its "target organ," one with the special "receptors" that allow it to recognize and respond to the hormone. But now, all organs are known to contain "estrogen receptors," and many of those same organs can produce very significant amounts of estrogen. The ovary, according to the classical doctrine, wouldn't be able to respond to estrogen. Oral contraceptive manufacturers used that idea to argue that excessive estrogen couldn't cause ovarian cancer, and in fact prevented it, by preventing ovulation. But the cells of the ovary do respond to estrogen, multiplying, and during *in vitro* exposure, developing a pre-cancerous appearance. For more than 20 years, there has been clear evidence that use of supplemental estrogen increases the incidence of ovarian cancer.

Related claims were made about estrogen and the prostate gland for more than 50 years: "Estrogen can't do anything to a male organ except to decrease its maleness," that is, it couldn't stimulate cell division or cause prostate cancer, but it would cause the prostate to shrink, and prevent prostate cancer. Many of those claims are still being made, and estrogen is still being prescribed to treat it by a large portion of the medical profession, though experiments are demonstrating estrogen's clear contribution to the prostate gland's degeneration into cancer.

The ovary has been a focus of several types of ideology in biology, and as a result real investigation of ovarian physiology has been retarded for 100 years. Weismann's genetic doctrine of the "isolation of the germ line" led to a false theory of ovarian aging, the egg-depletion theory. Despite the absence of evidence for the finite-egg-supply theory, and the increasing accumulation of evidence that eggs are continually produced in adult ovaries, many people still cling to the unfounded theory. The real nature of ovarian aging is very similar to the aging of any organ, and the extreme specialization of the ovary makes some of the issues clearer when we look at analogous processes in other organs, such as the prostate, or breast, or uterus, or the "adventitious organs" of inflammation and tumefaction.

In the normal ovary, under the influence of the pituitary follicle stimulating hormone, several pockets of fluid (primary follicles) begin forming in the ovary, and the largest of these follicles suppresses the development of the others, so that only one usually reaches full development. Under the influence of the pituitary luteinizing hormone, progesterone, and other substances, the ovum completes its meiosis, the follicle ruptures and the ovum along with the fluid containing a high concentration of estrogen is released. The cells that had surrounded and supported the ovum (granulosa cells) multiply to fill the space, forming the corpus luteum, the yellow body that produces mainly progesterone. The corpeus luteum is a thoroughly new organ that's produced periodically, under the influence of chains of interacting stimuli.

Warburg's main point about cancer was that it always has a "respiratory defect," causing it to produce lactic acid even in the presence of oxygen (a process called aerobic glycolysis), while oxygen causes normal cells to suppress lactic acid formation (this is called the Pasteur effect). Warburg believed that this defect in the cells' energy production system meant that it lacked the ability to perform many of its normal functions, but that it remained able to divide. He also believed that oxygen deprivation was one of many stressors that could damage the cells' respiratory system, and he showed that even very small tumors are usually very hypoxic. Other experimenters (including Hans Selye) found that mechanical barriers such as a glass tube or a bent piece of plastic film implanted into an animals

tissues would cause cancer to develop among the enclosed cells (following a period of atrophy).

There are a few normal situations in which aerobic glycolysis occurs--the retina, the ovarian follicle during its preparation for ovulation, the Sertoli cells of the testicle, which are involved in the maturation of sperm cells, and sometimes in the placenta. Except for the retina, these tissues are subject to strong stimulation by estrogen, which stimulates lactic acid formation while interfering with oxygen use. Aerobic glycolysis is associated with the formation of fatty acids (R.A. Walli, 1978), by the enzyme fatty acid synthase, which is increased by estrogen, and the activity of which corresponds to the malignancy of many types of cancer.

Estrogen and other stimuli can cause the formation of lactic acid even in the presence of oxygen (i.e., aerobic glycolysis). Lactic acid has some hormone-like actions, causing, for example, vasodilation and increased permeability of capillaries. It has been suggested that it has some involvement in the process of meiosis, in the formation of mature germ cells.

There are some compartments in the body that have very little oxygen, and that are damaged by increased oxygen. The thymus maintains a very low oxygen tension, but it has a strong Pasteur effect, so normally doesn't produce excess lactic acid. The testicle stops producing testosterone if the oxygen is increased too much. The vitreous body of the eye normally has low oxygen tension.

A special feature of the ovary is that the cells around the ovum are not only isolated from the blood supply, causing localized hypoxia, but they are also (unlike the hypoxic thymus) stimulated by estrogen.

In the expanded ovarian follicle, the ovum is a considerable distance from the closest blood vessels, and so it and its adjoining cells receive very little oxygen. Glucose diffuses into the follicle, and the granulosa cells around the ovum metabolize it into lactic acid. The concentration of lactate in the follicular fluid increases, along with estrogen, as the follicle matures, approaching ovulation. Immediately following ovulation, the granulosa cells multiply, filling the space that was formerly the follicle, and the blood vessels that had surrounded the follicle now infiltrate the developing corpus luteum, so that it receives an abundant oxygen supply as it begins forming progesterone.

The permutations of these variations in oxygen tension, glucose supply, and excitatory stimulation can account for a variety of developmental processes, and the resulting concentrations of lactic acid, carbon dioxide, fatty acids, and pH increase the range of formative possibilities. Carbon monoxide has the ability to mimic hypoxia even in the presence of oxygen.

Estrogen, in many different organs, increases the production of the enzyme heme oxygenase, which produces carbon monoxide, which inhibits respiration and also inhibits a variety of enzymes that use the heme group. (Tian, et al., 2003, 2004; Tschugguel, et al., 2001).

In the ovary, carbon monoxide increases the production of estrogen, but decreases the production of progesterone. An excess of estrogen, acting partly through the increased carbon monoxide, blocks the formation of progesterone, and prevents a successful ovulation.

These are just some of the interactions within the ovary that are similar to processes in the cancerization process wherever it occurs. Any inflamed tissue becomes subject to estrogenic stimulation, by the activation of enzymes, especially beta-glucuronidase, which cause estrogen to be deposited in the cells. Any hypoxic tissue, including inflammations of any sort, will express the heme oxygenase enzyme, producing carbon monoxide. Presumably, in the short term, these increases of estrogen and carbon monoxide have their adaptive functions, such as stimulating cell division for healing, and blocking some kinds of free radicals and excessive calcium uptake. But, as in the ovary, when the system isn't able to suppress them, they become self-sustaining, and begin to spread their influence to neighboring cells. Cancer cells are very resistant to injury from free radicals, which in normal cells accelerate the spontaneous dissolution called apoptosis, and carbon monoxide is one of their defense mechanisms, that makes them relatively immortal (Ghattas, et al., 2002).

When an organism is functioning normally and adapting to stresses, the operation of a functional system, including the part of the

nervous system that coordinates the function, causes that system to be stabilized, and to become more efficient, and even to grow. Work causes muscles and bones to enlarge and become stronger, learning causes the brain to grow. Chronic inflammations have some of the properties of a functional system, with participation of the nervous system, adjustments of the immune system, and changes in the circulatory system, except that the normal and desirable functions are progressively lost, rather than improved. The operation of the short term protective measures contribute, if they persist too long, to atrophy and fibrosis, and potentially, to disordered growth.

In some cases, we know that an excess of stimulation, in reaction to the organ's reduced functioning, promotes the growth and spread of a tumor, for example, prolactin contributes to breast cancer, thyrotropic hormone to thyroid cancer, and gonadotropin to ovarian cancer. Ovarian teratomas are now believed to be parthenogenic, deriving from an unfertilized ovum, and I have suspected that the direction of their development reflects the endocrine situation, for example when a teratoma consisting of thyroid tissue appears in a woman who has taken extremely big doses of iodine for a long time.

In the chronic inflammatory state that develops with stress and aging, besides the extrinsic stimuli that were the subject matter of classical endocrinology--pituitary hormones driving the ovaries, ovarian hormones driving the uterus, etc.--the inflamed tissues begin to stimulate themselves: The breast and uterus begin to synthesize estrogen, for example.

Some of the things produced by tumors, such as estrogen and carbon monoxide, appear to be the result of a short-term adaptive factor that becomes maladaptive when the system can't turn it off. It's generally assumed that when a tumor produces a hormone, its effects will necessarily be harmful, but sometimes it isn't clear whether they are harmful or beneficial, and in a few cases, they clearly seem to be beneficial.

Many cancers cause a great increase in the concentration of calcium in the blood, and this is often the result of the production of parathyroid hormone-related protein (PTH-rP) by the tumor. In some cases, PTH-rP can induce apoptosis by causing cells to take up calcium, but in other cases it is a survival factor, for example for nerve cells in the brain. Some experiments show that increased calcium in a tissue suppresses heme oxygenase and carbon monoxide (Zhang, et al., 2003, 2004). PTH-rP and the parathyroid hormone itself have some functions that overlap with those of vitamin D, which is now known to help to suppress many cancers.

Inhibitors of fatty acid synthase cause many types of cancer cells to die. Vitamin D, which stops the growth of breast, prostate, and bowel cancer cells, inhibits FAS (Qiao, et al., 2003). This could be another example of Zajicek's principle, since it has been discovered that prostate and other **cancer cells are able to create the active form of vitamin D.** Vitamin D also acts as an antiestrogen, and estrogen is a factor in the development prostate cancer, breast cancer, and many other types of cancer (Swami, et al., 2000; Demirpence, et al., 2001).

In some cancers, vitamin D operates through ceramide (Pirianov and Colston, 2001), Palmitic acid, is a product of FAS and a component of ceramide, which inhibits cancer cell growth.

Understanding the causes of tissue atrophy as a failure of energy that allows inflammation to become chronic, leading to a disorganized attempt to regenerate tissue and stabilize the system, our response to both atrophy and cancer should be to restore metabolic processes of the highest type, based on the oxidation of glucose with the production of carbon dioxide, rather than lactic acid and fatty acids, and to eliminate inflammation and its products that have disrupted the normal balance between cell renewal and cell elimination. Aspirin, by inhibiting the production of estrogen, of carbon monoxide, and of several cytokines and toxic lipid products, and by supporting normal respiration, helping to correct hyperglycemia, and suppressing lactate production, is an especially valuable therapy. Sacca et al., have recently (October, 2004) demonstrated that aspirin's anticancer effect appears to involve the inhibition of heme oxygenase.

Caffeine, by inhibiting FAS and sparing glucose, and inhibiting many of the toxic lipid

products and other inflammatory mediators, should have at least additive effects when combined with aspirin.

Vitamin D, by its antiestrogenic and antiinflammatory actions, and by suppressing FAS, parallels the effects of aspirin and caffeine in several ways.

Gelatin, by lowering serotonin, should help to prevent excessive activation of heme oxygenase and formation of carbon monoxide during injury or stress (on the role of serotonin: Sharma and Westman, 2003; Sharma, et al., 2003).

The lower incidence of, and mortality from, cancer at high altitudes might partly be explained by experiments that show that reduced atmospheric oxygen tension down-regulates heme oxygenase in human cells (Kitamuro, 2003).

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Ray Peat's Newsletter

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THE ARGUMENT:

Cancer is the result of ordinary physiological processes which become autonomous because of regulatory weaknesses in the organism.

Respiration is essential for the maintenance of the higher forms of life, and it is a respiratory defect, on both the cellular and the organismic levels, which allows cancer to persist and develop.

The heme group, because it serves many respiratory functions--hemoglobin, mitochondrial respiratory enzymes, steroid synthesizing enzymes, formation of thyroid hormone, detoxifying enzymes--is regulated in relatively primitive ways within each cell, and in more complex ways at higher organismic levels.

When the cell needs more respiratory energy, some fuel is diverted into the production of porphyrin, which is then turned into heme, which would normally provide for the efficient production of energy and protective factors.

When the efficient energy-producing systems are blocked, by injury, oxygen deficiency, toxins, or by the lack of one or more essential nutritional factors, heme production is activated.

Excess heme is destroyed by the enzyme heme oxygenase, which converts heme into biliverdin and carbon monoxide. Both of these factors have effects on the cell which are characteristic of cancer.

Estrogen, radiation, chemical carcinogens, and other forms of stress, activate the heme oxygenase enzyme.

Estrogen causes both porphyria and jaundice and is associated with increased formation of carbon monoxide. It inhibits many types of liver function, including detoxification.

The production of carbon monoxide by cancer cells can account for cancer's self-sustaining, "hereditary," property, without invoking genetic mutations which are now known to be consequences, rather than causes of cancer.

The production of carbon monoxide and biliverdin can account for many of the structural and biochemical abnormalities of cancer cells, and for their induction of abnormalities in adjacent cells.

"Genetic" theories of cancer have now reached a dead end, and the epigenetic, developmental-physiological approach remains as the only plausible description of cancer.

Carbon Monoxide, Stress, and Cancer: 1999 status

When we thoroughly understand cancer, we will be closer to understanding life itself.

Cancer, AIDS, and extreme hypothyroidism have several features in common--they cause tissue loss and organ damage, with immunodeficiency and intense activation of the stress hormones, including cortisol. In cancer and AIDS, a good case has been made for the primacy of stress-induced wasting as the main cause of death. Whatever one might believe to be the cause of cancer and AIDS, it is always good for the patient to prevent tissue damage from the stress associated with the sickness. Since the stress hormones primarily destroy tissues by the activation of specific proteases, the use of protease inhibitors for treating AIDS is probably helping to prevent tissue loss, as an unintended side effect. But in the case of cancer, there are good reasons for believing that metabolic dysregulations are the cause of the disease itself, as well as of the wasting symptoms.

When I wrote about carbon monoxide as a cancer hormone a few years ago, some people were confused, and I think that was because I didn't explain in detail how Otto Warburg's work made the idea seem so obvious.

In studying the pigments of cellular respiration (enzyme cofactors, including vitamin B2 and the cytochromes), Otto Warburg (1926) found that carbon monoxide, the respiratory poison, bound to some of the crucial pigments, and that light would free the pigment from the carbon monoxide, restoring respiration. Despite the fact that his work is described in all biochemistry textbooks, until very recently the toxicity of carbon monoxide was ascribed by medical texts only to its

effects on hemoglobin, preventing the delivery of oxygen to cells, rather than to its effects on the respiratory pigments in the mitochondria, as demonstrated by Warburg. Of the thousands of publications on the toxicity of carbon monoxide in recent decades, its effects on mitochondrial metabolism have hardly been investigated, because of the persepective that it was a poison coming from outside the body, and that its effect on hemoglobin was sufficient to cause death, so the question of its effect on the mitochondrion was medically irrelevant.

In his famous theory of cancer, Warburg argued that cancer was always characterized by "a respiratory defect," and he argued that many things could damage the respiratory system and lead to cancer. He and his colleagues over several decades showed that all the known causes of cancer produced the characteristic respiratory defect of cancer, in which cells would produce lactic acid even in the presence of normal levels of oxygen. This is called *aerobic glycolysis*, and in normal cells, the production of lactic acid is *anaerobic*, since the availability of oxygen suppresses the production of lactic acid, and causes carbon dioxide to be produced instead. (This effect of oxygen is called the Pasteur effect, and I think it is largely the production of carbon dioxide which accounts for it, though other things such as the level of ATP contribute to it.)

Warburg showed that chemical carcinogens, radiation, prolonged culture without adequate oxygen, and even vitamin B1 or B2 deficiency would promote first the characteristic cancer metabolism, and then actual cancerization. Most cells with the respiratory defect simply died, and it was those which could adapt to live with the defect which became cancerous. The tumor which results from a metabolic defect will "epigenetically," secondarily, develop chromosome imbalances, which may approximately coincide with the cells' transformation into cancer, and the conditions within the tumor will increase the tendency to produce mutations, which are not likely to be repaired in the extremely stressed state of the cells.

I think the reason Warburg didn't explore the role of carbon monoxide in cancer was simply that, during his lifetime, it wasn't recognized as something which is produced in the body. **Warburg had no reason to suspect that carbon monoxide would be produced by the cell exactly when the cell's respiratory apparatus was challenged. But since about 1971, carbon monoxide has been recognized as a normal product of the degradation of heme, approximately at the same time that it has become clear that respiratory distress on the cellular level stimulates both the synthesis and the degradation of heme.**

Unfortunately, after Warburg's death, there were no prestigious advocates of his theory, and his death coincided with America's "war on cancer," which consisted of giving huge public funding to the "cancer genetics" estrablishment, people who were congenitally hostile to the concept that cancer had knowable or controllable causes. Industry and medicine found it convenient to argue that people were responsible for their own diseases, in the sense that they inherited them, as a kind of mechanistic karma. *Mutations in the inherited genes were, by definition, "random," which gave them the virtue of being impossible to pin down to a specific, legally actionable, cause.*

The genetic, and thus "essential," nature of cancer justified the concept of treating it by killing it. (The procedure William Blake described 200 years ago as "curing the pox by cutting out the spots.") The doctrine of genetic causality indicated that only capital punishment could deal with the traitor-genes. Although these essentialists at first had rejected the idea that viruses could integrate themselves within our genes, after several years they realized that this idea meant that the infectious disease establishment could join forces with the genetics establishment. The new, highly funded "oncogene" establishment had absolute control over cancer research, and that direct control spread indirectly, like a malignancy, throughout academic and commercial biology.

Most people in the contemporary medical industry are so fond of the idea of DNA-mutation, followed by "clonal selection," to explain cancer, that they are able to ignore the many types of

evidence that show cancer to be a process of deterioration in a mass of cells, rather than a progression of a single cell through stages of DNA mutation.

This obsessive belief that "DNA causes everything" goes back to Weismannism, and the Neo-Darwinism that he founded by presenting his--purely arbitrary--arguments to eliminate the inheritance of acquired traits from the theory of evolution, and--*opposing Darwin*--to claim that Natural Selection was the only force in evolution. Weismannism, in its absolute rejection of the environmental adaptationism of Darwin and Lamarck, was almost a reversion to Preformationsim. In its insistence on the "isolation of the germline," or the *immortality of the germline* which was passed on in the germ cells of the gonads, Weismannism subscribed to the Preformationist belief that all future generations are contained in the germ cell, and its adherents tried to justify this by asserting that the *soma,* all the rest of the individual outside of the germ cells, was nothing more than a mortal shadow of the essential (genetic) immortal being, since the body was produced precisely by the **deletion** of the information contained in the germ cell. (This doctrine was behind the denial that animals could be cloned from the nucleus of body cells. Even after frogs, sheep, and cows were produced in this way, there were some people who couldn't accept the results as facts. The doctrine that "telomeric shortening" causes aging came straight out of Weismannism.)

Of course those ideas were false, nothing but an absurd application of Rationalist philosophy to biology to eliminate Darwin's "materialism," but the doctrine's importance is undeniable, since its direct influence can be seen in every university biology course and textbook of the 20th century.

It is this essentialist commitment of the cancer establishment that has made Warburg's work practically disappear from the academic culture. His demonstration that the cancer metabolism could be reversed by vitamins was a threat to the entire foundation of twentieth century essentialist medicine.

Poor Nutrition + Estro
= ↑ porphyrin

Because of my interest in the effects of light on the hormones and respiratory energy production, and my long-standing interest in Warburg's view of oxygen's role in evolution and cancer, and my awareness that *porphyrins** were at one time thought to be cancer hormones, it seemed obvious to think of carbon monoxide as a cancer hormone.

I happened to become acquainted with Leonell Strong, who developed the strains of cancer-prone mice that have been used in breast cancer research. ***Although he was a geneticist and bred the mice that demonstrated the inheritance of cancer, he also showed that simple therapeutic measures would not only prevent cancer in a susceptible individual, but would also prevent cancer in many generations of the treated animal's descendants.*** Strong discovered that estrogen and poor nutrition lead to overproduction of the porphyrin pigment, and contribute to the development of cancer. He showed that the liver was involved in the control of cancer. The Shutes, the Biskinds, and Alexander Lipshutz were at this time revealing other effects of estrogen that illuminated Strong's discoveries.

Besides Strong, who showed individual and hereditary avoidance of cancer, many other workers have demonstrated that "established" cancer cell lines can be induced to revert to normal tissue. Inheritance isn't indelibly fixed. A *physiological state* is passed on. Since carbon monoxide produces a respiratory defect, and is produced during respiratory deficiency, it is one of the factors which can account for the "heritability" of cancer. When cancer cells are implanted into a healthy host, they seldom gorw, but when implanted into a host who already has cancer, they grow. (Hakim, 1988.) The healthy host provides many restorative factors, the sick host provides additional harmful factors, but few restorative factors (Chekulaev, et al., 1987.)

*(*Porphyrins are the pigment molecules that include the heme of hemoglobin, of the respiratory cytochromes, the peroxidases including thyroid peroxidase, and of the P-450 enzymes which, among other things, produce steroid hormones.)*

One of the mysteries of public health is that people who drink alcohol live longer and are generally healthier than people who don't. 30 years ago, when I began studying Warburg's work, I heard about a man with inoperable cancer who, because of his hopeless condition, began living almost exclusively on hard liquor. Aftrer six months his doctor wondered why he was still alive, and a new operation revealed that there was no cancer.

In Warburg's view, cancer has a unique requirement for glucose, because of its "respiratory defect." The ability of cancer to consume large amounts of glucose means that the body interprets cancer as stress, since the waste of glucose is the key feature of stress. The body's response to decreasing glucose is to produce larger amounts of adrenal hormones, especially cortisol. Cortisol raises the blood glucose supply by converting tissue proteins into sugar. This hormonal response to the sugar appetite of cancer is the main cause of the wasting syndrome which makes cancer so serious, and which destroys the thymus gland, causing the immune system to lose its guidance. V. S. Shapot's work, showing the involvment of glucose and cortisol in cancer, provides part of the context for understanding the implications of Warburg's view of cancer as a "respiratory defect."

Alcohol has the ability to lower blood glucose, but it does it partly by suppressing the stress-induced secretion of cortisol, reducing the conversion of the body's proteins into glucose, and shifting metabolism toward fat as an energy source. Additionally, ethyl alcohol happens to detoxify carbon monoxide, "desorbing" it from the heme groups, somewhat as light does. These properties of alcohol have been studied in hospitalized patients. In terminal cancer patients, it was found to be extremely effective in protecting against the tissue wasting process. Even in alcoholics with liver cirrhosis, it was found to be protective to the liver, when added to a good diet.

Ordinary stress lowers blood sugar and produces lactic acid, because it uses energy faster than cells can produce it by way of efficient oxidative metabolism, and so sugar is inefficiently converted to lactic acid. This form of metabolism raises the cell's internal pH, intensifies its negative electrical charge, and causes it to take up water, and to alter its control of salts and other solutes; these changes may stimulate cell division, but they can also cause cell death, or adaptive modifications.

While the genetic, the metabolic, and the adaptive processes seem to be on very different "levels," if we are to think about them in realistic and productive ways, it's necessary to follow the ways in which they are integrated, and to see *gene regulation and metabolic responses to the environment as a continuous physical-chemical process.* The myth of the isolated immortal germline, and its derivative, the "Central Dogma" of molecular genetics, that sees information flowing only from the genes into the proteins, have kept most researchers from looking elsewhere for regulatory principles.

The idea of inheritance as a rigidly fixed system has made it easy to think of biology in terms of the "lock and key" analogy, in which an enzyme and its substrate, an antibody and its antigen, an organism and its niche, a gene and its inducer, etc., have a specific, fixed, mechanical relationship. However, even the simplest organisms have qualities that can seem more like a locksmith who with a little time can figure out how to open locks without a key. All biological systems are simultaneously regulated on more than one level, in a coherent and unified way.

The cell's framework, the "cytoskeleton," was demonstrated early in the 20th century, but the dogmatic view of the cell as "liquid enclosed by a membrane" caused it to be ignored by most biologists until the 1970s. The cytoskeleton is strongly influenced by respiratory distress and the hormones that are so closely associated with oxidative processes, estrogen and the porphyrin derivatives in particular.

The cytoskeleton includes a variety of filaments and tubelike structures. The microtubules make up the apparatus that separates the chromosomes during cell division. Estrogen can cause almost instantaneous changes in the cytoskeleton proteins and their interations with

have a variety of actions that tend to improve respiration.

Things that protect the bowel, such as raw carrots, have far-reaching effects on hormones and immunity. Eggs contain many protective and therapeutic factors, in spite of their excess of toxic unsaturated fats resulting from an unnatural diet; egg lecithin, for example, isn't immunosuppressive, as soybean lecithin is.

The last experiments of Leonell Strong, in which he found that certain combinations of nucleosides could cause the disappearance of cancer from the progeny of the treated animals, should be taken seriously. They relate to the heritable effects of hormone balance ("hormonal imprinting"), and so have implications far beyond the prevention of cancer.

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Endocrinology 1996 Nov;137(11):4536-41 **The cellular protooncogenes c-fos and egr-1 are regulated by prostacyclin in rodent osteoblasts and fibroblasts.** Glantschnig H, Varga F, Klaushofer K PGs are local regulators of various cellular functions. They exert their effects via specific PG receptor subtypes. **Induction of c-fos gene expression has been described for arachidonic acid and its metabolite PGE2.** We demonstrate that another very short half-lifed prostanoid metabolite, namely prostacyclin (PGI2), is a regulator of immediate-early genes. PGI2 transiently induced the growth-associated immediate-early genes c-fos and egr-1 in osteoblastic as well as fibroblastic cell lines. Furthermore, we showed that **PGI2 dose dependently stimulated new DNA synthesis in the osteoblastic cell line MC3T3-E1.** Although PGI2 is known to be a potent inducer of cyclooxygenases, we showed that this **pathway is not necessary for protooncogene induction by PGI2. Our data indicate a direct effect of PGI2 on immediate-early gene** expression, which does not depend on the synthesis of other prostanoids. Intracellular signal transduction mechanisms were studied with the protein kinase inhibitor H-7, a potent inhibitor of PGI2-induced c-fos expression. Experiments with phorbol esters revealed that protein kinase C activity is not obligatory for the effect of PGI2 on c-fos expression. We conclude from these results that PGI2, a rapidly inactivated prostanoid, has a major impact on cellular oncogene expression and growth in mesenchymally derived cells.

Proc Natl Acad Sci U S A 1998 Nov 10;95(23):13692-7 **Genetic instability of cancer cells is proportional to their degree of aneuploidy.** Duesberg P, Rausch C, Rasnick D, Hehlmann R III Genetic and phenotypic instability are hallmarks of cancer cells, but their cause is not clear. The leading hypothesis suggests that a poorly defined gene mutation generates genetic instability and that some of many subsequent mutations then cause cancer. Here we investigate the hypothesis that genetic instability of cancer cells is caused by aneuploidy, an abnormal balance of chromosomes. Because symmetrical segregation of chromosomes depends on exactly two copies of mitosis genes, aneuploidy involving chromosomes with mitosis genes will destabilize the karyotype. The hypothesis predicts that the degree of genetic instability should be proportional to the degree of aneuploidy. Thus it should be difficult, if not impossible, to maintain the particular karyotype of a highly aneuploid cancer cell on clonal propagation. This prediction was confirmed with clonal cultures of chemically transformed, aneuploid Chinese hamster embryo cells. It was found that the higher the ploidy factor of a clone, the more unstable was its karyotype. The ploidy factor is the quotient of the modal chromosome number divided by the normal number of the species. Transformed Chinese hamster embryo cells with a ploidy factor of 1.7 were estimated to change their karyotype at a rate of about 3% per generation, compared with 1.8% for cells with a ploidy factor of 0.95. Because the background noise of karyotyping is relatively high, the cells with low ploidy factor may be more stable than our method suggests. The karyotype instability of human colon cancer cell lines, recently analyzed by Lengnauer et al. [Lengnauer, C., Kinzler, K. W. & Vogelstein, B. (1997) Nature (London) 386, 623-627], also corresponds exactly to their degree of aneuploidy. We conclude that aneuploidy is sufficient to explain genetic instability and the resulting karyotypic and phenotypic heterogeneity of cancer cells, **independent of gene mutation.** Because aneuploidy has also been proposed to cause cancer, our hypothesis offers a common, unique mechanism of altering

water. Under the influence of estrogen, microtubules, for example, change their physical state and appear to dissolve. Experiments show that increasing amounts of estrogen cause progressively more severe disruptions of the mitotic apparatus, producing lopsided cell divisions. (When these abnormal "mitotic figures" are found in breast tissue, it means that cells are being killed by an excess of estrogen, but these dying cells are usually taken as "evidence of cancer.")

Biliverdin, produced along with carbon monoxide in the breakdown of heme, causes changes in other parts of the cytoskeleton, including the proteins in the nucleus which help to regulate the movements of nucleic acids.

Carbon monoxide, and other substances such as nitric oxide which also function as respiratory poisons, suppress energy production by the mitochondria, and this activates enzymes which cut DNA molecules, producing either DNA rearrangement, or apoptotic cell death.

All of these well established observations show the steps by which physiological reactions can lead to chromosomal and genetic abnormalities.

The steps toward cancer include chronic irritation, recognized for centuries as a cause of cancer; an inflammatory reaction activates enzymes that release estrogen. (Histamine, free fatty acids, prostaglandins, calcium and other products of inflammation are further promoted by estrogen, and synergize with it.)

Estrogen activates other inflammatory "acute phase" and stress-shock proteins, including heme oxygenase, which produces carbon monoxide and biliverdin. These are powerful protective and antioxidant factors making cells resistant to apoptosis and regulation.

Biliverdin (F. Paradisi, 1975) activates beta-glucuronidase, one of the main enzymes involved in the local release of estrogen.

In later stages, anemia and hemolysis are associated with CO and biliverdin production from the release of heme. (Anemia is seen in most patients with advanced cancer.) Biliverdin, combined with estrogen and hypoxia, alters the cytoskeleton, producing chromosome imbalances, causing mutations and activating the "oncogenes."

The respiratory defect of cancer interferes with the production of carbon dioxide. CO2 suppresses lactic acid formation, and is essential for all normal cell processes; it appears to be an important factor in producing cellular differentiation (Dictyostelium).

Estrogen promotes lactic acid formation, and promotes porphyrin synthesis, providing the material for forming heme and carbon monoxide. Besides causing porphyria, estrogen causes many other liver diseases, including cholestasis, the failure to release bile; the inhibition of carbon monoxide formation has been found to promote bile flow. Estrogen promotes the formation of the enzyme heme oxygenase, which forms carbon monoxide from heme.

Carbon monoxide increases the formation of cortisol, by stimulating ACTH release from the pituitary.

The stress response is self-sustaining on several levels. For example, stress increases the absorption of bacterial endotoxin from the intestine, which increases the estrogen level and synergizes with biliverdin and cortisol.

While estrogen does cause direct DNA damage, its clearest effect in carcinogenesis is on the cytoskeleton which regulates cell division, and defective cell division, rather than "gene mutation," is one of the important steps in the progression of cancer (Rubin, Duesberg).

Cancer cells are protected against the body's ability to destroy them, by the antioxidant functions of carbon dioxide and biliverdin..

The multilevel physiological nature of cancer calls for a multilevel physiological approach to its prevention and cure.

This would include antiestrogen regimes, antiinflammatory and antihistamine factors (histamine interacts closely with nitric oxide and carbon monoxide), adequate nutrition, carbon dioxide, and specific anti-carbon monoxide therapies (such as light, alcohol, and possibly the minerals which convert porphyrin into compounds that inhibit the production of carbon monoxide), and methods to decrease nitric oxide formation and to restrain cortisol production, since these promote the formation of carbon monoxide. **One of the most interesting approaches to inhibiting carbon monoxide production is to use vitamin B12, as hydroxocobalamin, as an antidote to nitric oxide, preventing the nitric oxide from stimulating the formation of heme oxygenase.** Wherever carbon monoxide mediates a biological malfunction, as in aquired immunodeficiency, Alzheimer's disease, and cancer, vitamin B12 seems to have a place as a detoxicant.

Progesterone and thyroid have several desirable properties that make them generally useful in cancer prevention and therapy. The shorter-chain saturated fatty acids contained in coconut oil have several beneficial effects. Aspirin and vitamin E

and simultaneously destabilizing normal cellular phenotypes.

Proc Natl Acad Sci U S A 1997 Dec 23;94(26):14506-11 **Aneuploidy correlated 100% with chemical transformation of Chinese hamster cells.** Li R, Yerganian G, Duesberg P, Kraemer A, Willer A, Rausch C, Hehlmann R Aneuploidy or chromosome imbalance is the most massive genetic abnormality of cancer cells. It used to be considered the cause of cancer when it was discovered more than 100 years ago. Since the discovery of the **gene,** the aneuploidy hypothesis has lost ground to the hypothesis that mutation of cellular genes causes cancer. According to this hypothesis, cancers are diploid and aneuploidy is secondary or nonessential. Here we reexamine the aneuploidy hypothesis in view of the fact that nearly all solid cancers are aneuploid, **that many carcinogens are nongenotoxic,** and that mutated genes from cancer cells **do not transform diploid human or animal cells.** By regrouping the gene pool-as in speciation-aneuploidy inevitably will alter many genetic programs. This genetic revolution can explain the numerous unique properties of cancer cells, such as invasiveness, dedifferentiation, distinct morphology, and specific surface antigens, much better than gene mutation, which is limited by the conservation of the existing chromosome structure. To determine whether aneuploidy is a cause or a consequence of transformation, we have analyzed the chromosomes of Chinese hamster embryo (CHE) cells transformed in vitro. This system allows (i) detection of transformation within 2 months and thus about 5 months sooner than carcinogenesis and (ii) the generation of many more transformants per cost than carcinogenesis. To minimize mutation of cellular genes, we have used nongenotoxic carcinogens. **It was found that 44 out of 44 colonies of CHE cells transformed by benz[a]pyrene, methylcholanthrene, dimethylbenzanthracene, and colcemid, or spontaneously were between 50 and 100% aneuploid.** Thus, aneuploidy originated with transformation. Two of two chemically transformed colonies tested were tumorigenic 2 months after inoculation into hamsters. The cells of transformed colonies were heterogeneous in chromosome number, consistent with the hypothesis that aneuploidy can perpetually destabilize the chromosome number because it unbalances the elements of the mitotic apparatus. Considering that all 44 transformed colonies analyzed were aneuploid, and the early association between aneuploidy, transformation, and tumorigenicity, we conclude that aneuploidy is the cause rather than a consequence of transformation.

Proc Natl Acad Sci U S A 1997 Sep 2;94(18):9614-9 **Dominant transformation by mutated human ras genes in vitro requires more than 100 times higher expression than is observed in cancers.** Hua VY, Wang WK, Duesberg PH The gene-mutation-cancer hypothesis holds that mutated cellular protooncogenes, such as point-mutated proto-ras, "play a dominant part in cancer," because they are sufficient to transform transfected mouse cell lines in vitro [Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J. D. (1994) Molecular Biology of the Cell (Garland, New York)]. However, in cells transformed in vitro mutated human ras genes are expressed more than 100-fold than in the cancers from which they are isolated. In **view of the discrepancy between the very low levels of ras transcription in cancers and the very high levels in cells transformed in vitro,** we have investigated the minimal level of human ras expression for transformation in vitro. Using point-mutated human ras genes recombined with different promoters from **either human metallothionein-IIA or human** fibronectin or from retroviruses we found dominant in vitro transformation of the mouse C3H cell line only with ras genes linked to viral promoters. These ras genes were expressed more than 120-fold higher than are native ras genes of C3H cells. The copy number of transfected ras genes ranged from 2-6 in our system. In addition, nondominant transformation was observed in a small percentage (2-7%) of C3H cells transfected with ras genes that are expressed less than 20 times higher than native C3H ras genes. Because over 90% of cells expressing ras at this moderately enhanced level were untransformed, **transformation must follow either a nondominant ras mechanism or a non-ras mechanism.** We conclude that the mutated, but normally expressed, ras genes found in human and animal cancers are not likely to "play a dominant part in cancer." The conclusion that mutated ras genes are **not sufficient or dominant** for cancer is directly supported by recent discoveries of **mutated ras in normal animals, and in benign human tissue, "which has little potential to progress" [Jen, J., Powell, S. M., Papadopoulos, N., Smith, K. J., Hamilton, S. R., Vogelstein, B. & Kinzler, K. W. (1994) Cancer Res. 54, 5523-5526]. Even the view that mutated ras is necessary for cancer is hard to reconcile with (i) otherwise indistinguishable cancers with and without** ras mutations, (ii) metastases of the same human cancers with and without ras mutations, (iii) retroviral ras genes that are oncogenic without point mutations, and (iv) human tumor cells having spontaneously lost ras mutation but not tumorigencity.

Proc Natl Acad Sci U S A 1990 Dec;87(24):10005-10009 **Physiological induction and reversal of focus formation and tumorigenicity in NIH 3T3 cells.** Rubin AL, Arnstein P, Rubin H. NIH 3T3 cells undergo morphological transformation in response to conditions of constrained growth, such as occur in low serum concentrations or at confluence. Transformation is expressed in a small fraction of the cells by the appearance of discrete foci of multiplying cells on a confluent monolayer of quiescent cells. We isolated and expanded cell populations from three dense and three light foci. Cells from each of these populations efficiently reproduced foci of the same morphotype when grown on a background of nontransformed NIH 3T3 cells. Using cultures derived from one of the dense foci (subline D/2), we found that the number of focus-forming units was stable and the cells remained tumorigenic when they were subjected to repeated thrice-weekly passage in 2% calf serum. However, equivalent passage in 10% calf serum

eventually rendered the cells incapable of both focus production and tumor formation. **The results show that the capacity to produce tumors as well as morphological transformation are produced as a response to physiological constraints of growth and/or metabolism in the absence of carcinogens and that both properties can be reversed by lifting the constraints. This behavior is typical of an adaptational response and, taken together with other supporting evidence, shows that tumorigenesis does not require conventional genetic alteration.** Published erratum appears in Proc Natl Acad Sci U S A 1991 Apr 15;88(8):3510

J Surg Oncol 1974;6(3):191-195 **The transitory nature of a transmissible entity controlling the growth of a spontaneous tumor in mice.** Strong LC, Matsunaga H

J Surg Oncol 1974;6(1):29-38. **"Studies on the effects of adenosine upon tumor growth in mice."** Strong, L.C., Ishmael D.

Cytobios 1973 Jul;7(28):253-257 **Effect of 5-methyl-cytidine on growth and regression of spontaneous tumours in mice.** Strong LC, Matsunaga H

J Surg Oncol 1973;5(2):181-188 **Comparative effect of three nucleosides on suppression of cancer growth in mice.** Strong LC, Matsunaga H

Cytobios 1975;12(45):13-18 **An inverse correlation (dose-response between 5-methyl-cytidine and the fate of spontaneous tumours in mice.** Strong LC, Matsunaga H Tumour-bearing mice, 248 in number, have been injected with 5-methyl-cytidine dissolved in physiological salt solution. The mice were divided into 5 series depending upon the amount of 5-methyl-cytidine they received. Mice of a successive series received 43.2, 28.8, 14.4 and 7.2 mg/kg body weight. There was a progressive increase in the percentage of mice showing regression of tumours in the successive series, as follows: 45%, 50%, 65%, 60%, and 67.8% respectively, giving an average percentage of regressions of 59.7%. The incidence of mice developing multiple primary tumours increased in the same successive series respectively as follows: 25%, 43.8%, 58.3%, 73.3%, and 70%, thus giving an average of 58.3%. The evidence obtained indicates an inverse correlation (dose-response) between the amount of the 5-methyl-cytidine injected and the percentage of regressions of spontaneous tumours.

J Surg Oncol 1975;7(5):367-373 **Further studies on a transmissible entity in relation to the control of cancer in mice.** Strong LC, Matsunaga H Tumor-bearing mice of the C3H/ST inbreds were used in this investigation. Of the 598 mice, 290 were controls, 248 received injections of 5-methyl cytidine dissolved in physiological salt solution, and 60 received injections of three nucleosides - adenosine, 6-methyl adenosine, and 5-methyl cytidine - also dissolved in physiological salt solution. The mice were divided into 6 groups based upon the number of generations of descent from a mouse injected with an alcohol-soluble liver extract. The criterion of tumor growth is the average increment of growth at the 20th observation period in the 7th week (3 per week). There is a cumulative inhibition of tumor growth, compared with controls, when 5-methyl cytidine is added to the effect of a transmissible entity which occurs in the lineal descendants of a tumor-bearing mouse injected with an alcohol-soluble liver extract and when the combination of three nucleosides in the same ratio of molar concentrations as in the liver extract is added to the effect of the transmissible entity.

J Surg Oncol 1975;7(6):531-534 **An inverse dose response of 5-methyl cytidine on multiple primary spontaneous tumors and their regressions in mice.** Strong LC, Matsunaga H Ten series mice of C3H/ST inbreds with spontaneous tumors have received 5-methyl cytidine (total 500 mice). Graded single doses of (1) 3.86, (2) 2.57, (3) 2.06, (4) 1.54, (5) 1.03, (6) 1.54, (7) 1.03, (8) 0.51, (9) 0.26, and (10) 0.13 mg/injection (three times weekly) were used. In series 1-5 the 5-methyl cytidine was dissolved in distilled water, and in series 6-10, the nucleoside was dissolved in physiological salt solution. In doses administered, series 4-5 overlapped with series 6-7. The number of mice that showed a regression of tumor increased in the successive series (48%-63% in series 1-5 and 25%-73% in series 6-10). As the number of mice with regressing tumors increased, the percentage of mice showing multiple primary tumors also increased. The administration of the nucleoside in physiological salt solution altered the inhibitory effect of 5-methyl cytidine on spontaneous tumors. For example, in physiological salt solution the 0.51 mg/injection gave as much inhibitory action as 1.03 mg/injection in distilled water. An inverse dose response is thus indicated between the amount of 5-methyl cytidine injected and the inhibition of spontaneous tumors in mice (percentage of regression and number of multiple primary spontaneous tumors are the criteria of inhibition considered).

Cytobios 1976;17(67-68):177-181 **A second method for induction of a transmissible entity in the control of cancer in mice.** Strong LC, Matsunaga H Spontaneous tumour-bearing mice of the C3H/St and subline C3HB/St inbred strains received injections of three nucleosides, adenosine, 6-methyl adenosine, and 5-methyl cytidine, prepared in the **same molecular concentration as they had occurred in an alcohol-soluble liver extract which in previous work had suppressed tumour growth.** Two transmissible entities appear to be present and they show different degrees of effect upon the growth and regression of spontaneous tumours of mammary gland origin (adenocarcinoma). The first transmissible entity (TE) occurred in the lineal descent of mice following injection of the liver extract. The second entity (TE2) appeared following injection of 5-methyl cytidine. TE manifested its maximum effect in suppressing cancer in mice during the 20th generation of a lineal descent following the injection of the original liver

extract into a mother of the cancer proband. TE2 appears to be optimal in controlling cancer in the F11 generation of a second lineal descent derived from an original cancer proband of the C3H/St inbred strain injected with 5-methyl cytidine.

J Surg Oncol 1977;9(1):99-103 **Increased effect of a transmissible entity on the control of cancer in C3 H/St mice.** Strong LC, Matsunaga HThree hundred and seventy-one mice of the C3H/St inbreds bearing spontaneous tumors of mammary gland origin have been used in this experiment. All mice studied were lineal descendents of a tumor-bearing mouse which had been injected with a liver extract. In this descent there appears to be a transmissible entity presumably induced by the injection of the liver extract. Following 15 generations of inbreeding after the appearance of a transmissible entity, a second sudden reversal of effect on cancer growth in mice has been indicated. This change has progressively altered the growth of cancer from a very low effect to a maximal effect, i.e., to a complete regression of a high percentage of the tumor. The maximal effect of the transmissible entity is the complete suppression of the growth of cancer during, at least, through the 25th period of observation, thus producing negative values of tumor growth. All these effects of the growth and fate of spontaneous tumors of mammary gland origin in mice have been obtained in a single lineal descent of C3H/St inbreds without resorting to any outcross.

J Surg Oncol 1972;4(3):248-254 **Comparison of the effect of three nucleosides and a liver emulsion upon the inhibition of cancer in mice.** Strong LC, Matsunaga H.

J Surg Oncol 1972;4(5):528-532 **5-Methyl-cytidine as an inhibitor of spontaneous cancer in mice.** Strong LC, Matsunaga H.

Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 1971 Feb 26;75(3):225-228 **What is a control for cancer in mice?** Strong LC, Matsunaga H.

J Surg Oncol 1971;3(4):467-473 **The stimulation and inhibition of the growth capacities of spontaneous tumors of mammary gland origin in mice (adenocarcinomata).** Strong LC, Matsunaga H.

J Surg Oncol 1971;3(4):369-378 **The effect of 'aging' of an inhibitor of spontaneous tumors in mice.** II. Observations at aging from 101-1346 days. Strong LC, Matsunaga H.

J Surg Oncol 1970;2(4):363-372 **A "transmissible entity" in the control of cancer in mice.** Strong LC, Matsunaga H.

Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 1969;72(1):32-35 **Studies of the regression of spontaneous adenocarcinomata in mice.** Strong, L.C.

Nature 1968 Oct 19;220(164):282-283 **Effect of neomycin on an inhibitor of spontaneous tumors in mice.** Strong, L.C.

Lav Ist Anat Istol Patol Perugia 1966;26(1):5-13 **Why I originated the inbred strains of mice.Strong LC.**

Am J Physiol 1997 May;272(5 Pt 1):G1268-75. **Endogenous carbon monoxide suppression stimulates bile acid-dependent biliary transport in perfused rat liver.** Sano T, Shiomi M, Wakabayashi Y, Shinoda Y, Goda N, Yamaguchi T, Nimura Y, Ishimura Y, Suematsu M This study aimed to investigate whether carbon monoxide (CO), a product of heme oxygenase that degrades protoheme IX, serves as an endogenous modulator for biliary transport. To that end, effects of zinc protoporphyrin IX (ZnPP), a heme oxygenase inhibitor, on the biliary transport were tested in perfused rat liver. Perfusion of 1 microM ZnPP abolished detectable levels of CO in the venous perfusate and increased bile acid-dependent bile output accompanying an increased secretion of bile salts. The ZnPP-induced choleresis coincided with a reduction of tissue guanosine 3',5'-cyclic monophosphate (cGMP) levels and a decrease in vascular conductance. On administration of 2.5 microM CO, ZnPP-elicited choleresis, decreases in vascular conductance, and cGMP levels were all attenuated. Treatment with 1 microM 8-bromoguanosine 3',5'-cyclic monophosphate (8-BrcGMP) partly attenuated the **ZnPP-induced choleresis** in concert with repression of vascular conductance. Furthermore, treatment of the liver with methylene blue, a guanylate cyclase inhibitor, evoked a choleresis similar to that induced by ZnPP. **Thus endogenous CO suppression stimulates the biliary transport in part through a cGMP-dependent mechanism.**

Biochem Soc Trans 1997 Aug;25(3):406S **Does carbon monoxide inhibit cytochrome oxidase in vivo?** Davies NA, Trikkas C, Cooper CE.

Urology 1996 May;47(5):727-33 **Expression of heme oxygenase-1 (HSP32) in human prostate: normal, hyperplastic, and tumor tissue distribution.** Maines MD, Abrahamsson PA OBJECTIVES. Heme oxygenase isozymes, HO-1 and HO-2, are members of the stress/heat shock (HSP) family of proteins, with the known function of cleaving the heme molecule to biliverdin, iron, and carbon monoxide. The aim of this study was to examine the pattern of tissue expression of HO-1 in the humanprostate under different states of proliferation and differentiation and to investigate whether the pattern differs between these states. METHODS. Presently, we have determined the pattern of tissue expression of the stress-inducible isozyme, HO-1 (HSP32), in human prostate under normal and pathologic conditions, by immunohistochemistry, using polyclonal antibodies, and have measured HO-1 and HO-2 mRNA levels in normal prostate and benign prostatic hyperplasia (BPH) by Northern blotting. The activity of prostate to

catalyze heme degradation was also assessed. RESULTS. In normal and BPH tissue, columnar epithelial cells of acini and ducts and cells in stroma displayed HO-1 immunoreactivity; in all cells, perinuclear staining was prominent. In BPH tissue, however, a more intense staining of the epithelial cells occurred, with notable staining of the basal cells. In undifferentiated malignant tumors, intense HO-1 staining was manifest in nearly all tumor cells, and also in the epithelial lining of blood vessels. HO-1 in the prostate tissue was found catalytically active and oxidatively cleaved the heme molecule (Fe-protoporphyrin IX) to biliverdin. Northern blot analysis shows that two forms of HO are present in the human prostate. Compared with normal tissue, predominantly hyperplastic tissue demonstrates a pronounced increase in the approximately 1.8 kb mRNA that hybridizes to the rat HO-1 probe. The levels of two transcripts, approximately 1.3 and approximately 1.7 kb, that hybridize to the rat HO-2 probe are not increased in BPH tissue. CONCLUSIONS. **The finding that HO-1 expression is increased in BPH and malignant prostate tissue is consistent with a role for this stress protein in the pathogenesis of BPH and prostate cancer; in the context of iron metabolism, an argument is made in support of this possibility.**

Sangyo Igaku 1990 Jan;32(1):33-40 **[Effects of lead on drug metabolizing enzymes, cytochrome P-450 and hemeoxygenase in rats].** [Article in Japanese] Harada K, Ohmori S, Nagano M, Miura H "In a supplementary experiment, lead was found to decrease the contents of heme in the **microsome and to increase the activity of hemeoxygenase. "**

Cancer Res 1991 Feb 1;51(3):974-8 **Induction of heme oxygenase: a general response to oxidant stress in cultured mammalian cells.** Applegate LA, Luscher P, Tyrrell RM. Accumulation of heme oxygenase mRNA is strongly stimulated by treatment of cultured human skin **fibroblasts with ultraviolet radiation, hydrogen peroxide, or the sulfhydryl reagent sodium arsenite (S. M.** Keyse and R. M. Tyrrell. Proc. Natl. Acad. Sci. USA, 86: 99-103, 1989). Since this will result in a transient reduction in the prooxidant state of cells, the phenomenon may represent an important inducible antioxidant defense mechanism. To examine the generality of the response, we have measured the accumulation of the specific mRNA in a variety of human and mammalian cell types after inducing treatments. Induction by sodium arsenite is observed in all additional human cell types tested. This includes primary epidermal keratinocytes and lung and colon fibroblasts as well as established cell lines such as HeLa, TK6 lymphoblastoid, and transformed fetal keratinocytes. Strong induction of heme oxygenase mRNA is also observed following sodium arsenite treatment of cell lines of rat, hamster, mouse, monkey, and marsupial origin. The agents which lead to induction in cultured human skin fibroblasts fall into two categories: (a) those which are oxidants or can generate active intermediates (ultraviolet A radiation, hydrogen peroxide, menadione, and the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate); (b) agents which are known to interact with or modify cellular glutathione levels (buthionine sulfoximine, sodium arsenite, iodoacetamide, diamide, and cadmium chloride). These observations strongly support the hypothesis that induction of the enzyme is a general response to oxidant stress in mammalian cells and are consistent with the possibility that the cellular redox state plays a key role.

Carcinogenesis 1992 Feb;13(2):227-32 **Endogenous glutathione levels modulate both constitutive and UVA radiation/hydrogen peroxide inducible expression of the human heme oxygenase gene.** Lautier D, Luscher P, Tyrrell RM Swiss Induction of the expression of the mammalian heme oxygenase gene appears to be a general response to oxidant stress. In view of the role of glutathione in protecting cells against solar UVA radiation and other forms of oxidant stress, we have investigated the relationship between intracellular glutathione levels and the inducibility of the human heme oxygenase gene after treatment of populations of cultured skin fibroblasts with either UVA radiation or hydrogen peroxide. We observe a clear relationship between cellular glutathione status and both the constitutive and oxidant-inducible accumulation of heme oxygenase mRNA. Glutathione depletion may lead to enhanced gene expression either as a result of the potentiated accumulation of active oxygen intermediates or as a result of the direct influence of glutathione on a critical target involved in signal transduction.

Bull Cancer 1990;77(5):479-83 **[Modification of the cellular cytoskeleton and hepatic tumor promotion].** [Article in French] Decloitre F, Martin M, Ouldelhkim M, Nizard C. Non transformed epithelial hepatic cells (established cell line and adult rat hepatocytes) treated by liver **tumor promoters, phenobarbital and biliverdin,** for 24 and 48 h showed a fragmentation and loss of F-actin and a depolymerisation of microtubules. This pattern closely resembles that of transformed cells which were not susceptible to the action of promoters. In liver preneoplastic nodules obtained from rats submitted to an initiation-promotion process, actin almost completely disappeared with the concomitant appearance of a characteristic enzymatic pattern rich in GGT and GST-P. Therefore, cytoskeleton of hepatic cells is a target for tumor promoters and could play a role in promotion mechanism.

J Biochem (Tokyo) 1997 Jun;121(6):1162-8 **Possible implications of the induction of human heme oxygenase-1 by nitric oxide donors.** Takahashi K, Hara E, Ogawa K, Kimura D, Fujita H, Shibahara S. To explore the involvement of nitric oxide (NO) in the induction of heme oxygenase-1, an essential enzyme in heme catabolism, we studied the effects of NO donors on the expression of heme oxygenase-1 **mRNA in HeLa human cervical cancer cells. Treatment with each of three NO donors, sodium nitroprusside, 3-morpholinosydnonimine, and S-nitroso-L-glutathione, caused noticeable increases in**

the expression levels of heme oxygenase- mRNA, but not heme oxygenase-2 mRNA. On the other hand, nitrite or 8-bromo cGMP exerted no noticeable effect on the levels of heme oxygenase-1 mRNA. We showed that sodium nitroprusside also increased the **levels of heme oxygenase-1 protein.** The sodium nitroprusside-mediated increase in heme oxygenase-1 mRNA levels was abolished by treatment with actinomycin D. The expression levels of heme oxygenase-1 mRNA were also **increased by NO donors in human melanoma and neuroblastoma cell lines.** Thus, the observed induction of heme oxygenase-1 may represent an important response to NO or NO-related **oxidative stress.** The half lives of heme oxygenase-1 and heme oxygenase-2 mRNAs were estimated to be about 3.2 h and more than 5 h, respectively.

Ann N Y Acad Sci 1998 May 1;840:249-61 **Acute and subacute effects of endotoxin on hypothalamic gaseous neuromodulators.** Kostoglou-Athanassiou I, Jacobs RA, Satta MA, Dahia PL, Costa A, Navarra P, Chew SL, Forsling ML, Grossman, A.B.

Steroids, 1998, 63(5-6):252-6, **Neuroendocrine mechanisms underlying the control of gonadotropin secretion by steroids.** Mahesh VB, Brann DW. There is considerable evidence that although estradiol may trigger the preovulatory surge of gonadotropins, progesterone is required for its full magnitude and duration and that glucocorticoids bring about selective follicle-stimulating hormone release. The luteinizing hormone-releasing hormone (LHRH) neuron does not have steroid receptors and is regulated by excitatory amino acid neurotransmission. **Steroids do not appear to modulate excitatory amino acid receptors directly but increase release of glutamate in the preoptic area. This may be due to the suppression by steroids** of the enzyme glutamatic acid decarboxylase67 that converts glutamate into GABA. NMDA receptors colocalize with nitric oxide synthase-containing neurons that surround the LHRH neurons in the preoptic area and intersect the LHRH fibers in the median eminence. Other potential novel pathways of LHRH release that are currently being explored include carbon monoxide generated by the action of heme oxygenase-2 on heme molecules and bradykinin acting via bradykinin B2 receptors.

Biochem Biophys Res Commun 1997 Dec 18;241(2):215-20 **Involvement of the heme oxygenase-carbon monoxide pathway in keratinocyte proliferation.** Clark JE, Green CJ, Motterlini R. It has been suggested that nitric oxide (NO), a small gaseous molecule with a multiplicity of cellular functions, plays an important part in the regulation of cellular proliferation. We have examined the effect of the NO donor sodium nitroprusside (SNP) on heme oxygenase-1 (HO-1) expression in human **epidermal keratinocytes and investigated the contribution of the heme oxygenase pathway in the control of** keratinocyte proliferation. Incubation of keratinocytes with 0.5 mM SNP resulted in a **2.5-fold increase in heme oxygenase activity which was reflected by a significant increase in HO-1** protein expression, as measured by Western blot. This effect was associated with a **200% increase in keratinocyte proliferation.** The proliferative effect of the NO donor was totally abolished by co-incubation of SNP with tin protoporphyrin IX, a potent inhibitor of heme oxygenase, or hydroxocobalamin, a NO scavenger. These results suggest that the heme oxygenase pathway is involved in keratinocyte proliferation mediated by NO.

J Neuroimmunol 1998 Jun 1;86(1):104-9 **Endotoxin stimulates an endogenous pathway regulating corticotropin-releasing hormone and vasopressin release involving the generation of nitric oxide and carbon monoxide.** Kostoglou-Athanassiou I, Costa A, Navarra P, Nappi G, Forsling ML, Grossman AB.

Ann N Y Acad Sci 1998 May 1;840:249-61 **Acute and subacute effects of endotoxin on hypothalamic gaseous neuromodulators.** Kostoglou-Athanassiou I, Jacobs RA, Satta MA, Dahia PL, Costa A, Navarra P, Chew SL, Forsling ML, Grossman AB.

Cell Biol Toxicol 1990 Jan;6(1):23-34 **Modifications of microfilaments and microtubules induced by two hepatic tumor promoters, phenobarbital and biliverdin in non-transformed and transformed hepatic cell lines.** Decloitre F, Lafarge-Frayssinet C, Martin M, Frayssinet C. "Microfilaments and microtubules are components of the cytoskeleton which could be implicated in neoplastic transformation. We studied the effect of **two hepatic tumor promoters, phenobarbital (PB) and biliverdin** (BV), on microfilaments and microtubules of non-transformed (Cl3) and transformed (FV) hepatic epithelial cells. Cl3 non-transformed cells cultured in the presence of I X 10(-6) M BV for 48 h showed a loss of F-actin, fragmentation of actin and the appearance of star-like structures in the cytoplasm, as well as loosening of the peripheral bundle of actin, and some ruffling of cell membranes." "BV and PB also produced in these cells modifications of microtubules characterized by a disappearance of centrosome staining in numerous cells, a condensed ring of tubulin around the nucleus and a depolymerized aspect of the microtubular network. All these modifications of microfilaments and microtubules closely resembled those observed in FV transformed cells in the absence of any treatment (Solvent DMSO only). We did not observe an effect of BV and PB on FV cells. The present data demonstrate that the cytoskeleton of non-transformed epithelial liver cells is sensitive to the action of liver tumor promoters suggesting that it might play a role as to yet be defined in the promotion mechanism. "

Bull Cancer 1990;77(5):475-8 **[Oncogenes and tumor promotion].** [Article in French] Lafarge-Frayssinet C, Frayssinet C. We have studied the effects of 2 hepatic promoters: an exogenous one:phenobarbital, and an endogenous **one biliverdin (a bile pigment) on the expression of 3 oncogenes c-Ki-ras, c-fos and c-myc involved in**

growth process, differentiation and tumorigenesis for the liver. This work was done: 1) in vitro using epithelial liver cell strains originated from 10-day old rats; 2) in vivo using regenerating liver after partial hepatectomy, as well as preneoplastic nodules obtained by the Solt and Farber procedure. In all cases we have shown an important overexpression of the oncogenes.

Cell Mol Biol 1981;27(2-3):77-82 **Enhancement of DNA synthesis by biliverdin in a non-transformed liver cell strain.** Lafarge-Frayssinet C, Morel-Chany E, Trincal G, Frayssinet C Cancer Lett 1983 Apr;18(3):277-82 **Promoting effect of biliverdin for liver cells initiated by aflatoxin B1.** Lafarge-Frayssinet C, Morel-Chany E, Trincal G, Frayssinet C In this paper we have studied the participation of biliverdin, a bile pigment produced from hemoglobin catabolism, in a two-stage carcinogenesis model using hepatic cells in culture. The initiation was realised by a short term exposure to low doses of aflatoxin B1. The cells were then cultivated in the presence of biliverdin in the medium. We observed that biliverdin increased the rate and the efficiency of neoplastic transformation of cells. **These results suggest that biliverdin may act as a promoting substance.**

Cancer Lett 1989 Mar;44(3):191-8 **Over expression of proto-oncogenes: ki-ras, fos and myc in rat liver cells treated in vitro by two liver tumor promoters: phenobarbital and biliverdin.** Lafarge-Frayssinet C, Frayssinet C Among the liver cell strains established in the laboratory from the liver of 10-day-old rats, some of them (FV) underwent spontaneous neoplastic transformation after a number of subcultures. However, one (Cl3) had maintained a non-transformed phenotype (persistence of contact inhibition, lack of growth in soft agar and of gamma glutamyltranspeptidase activity). These cells were grown either for a short time (48 h) or a longer time (3 weeks) in the presence of two liver tumor promoters: phenobarbital (0.2 x 10(-3) M) or biliverdin (10(-6) M). Total RNA was analysed by dot blot and Northern blot, then hybridized with ki-ras, fos and myc probes, previously labelled with 32P by nick translation. The three oncogenes were well expressed by the two strains but while an over-expression was observed for the Cl3 non-transformed cells when they were grown in presence of phenobarbital or biliverdin, the FV-transformed cells were not sensitive to the two promoters.

Pathol Biol (Paris) 1975 Feb;23(2):101-5 **A cytochemical study of some enzyme activities in biliverdin-treated cell cultures.** Paradisi F, Graziano L, de Ritis F The authors studied the modifications of the activities of some enzymes in cell cultures submitted to the action of biliverdin. This biliary pigment rapidly induces a **remarkable increase in alkaline phosphatase and ATP-ase activities and subsequently, an activation of acid phosphatase and beta-glucuronidase.** On the contrary, 5'-nucleotidase and glucose-6-phosphatase activities remain unchanged. These results are discussed and compared with those obtained in our and other laboratories by using unconjugated bilirubin on different biological substrates.

Mol Pharmacol 1997 Oct;52(4):590-9 **Aryl hydrocarbon receptor-dependent induction of cyp1a1 by bilirubin in mouse hepatoma hepa 1c1c7 cells.** Sinal CJ, Bend JR "Heme metabolism normally involves enzymatic conversion to biliverdin and subsequently to bilirubin, catalyzed by heme oxygenase and biliverdin reductase, respectively. We examined the ability of exogenously added hemin, biliverdin, or bilirubin to regulate Cyp1a1, an enzyme that may be active in bilirubin elimination. A substantial dose-dependent increase in Cyp1a1 mRNA occurred after treatment of Hepa 1c1c7 cells with either of the three compounds. This increase was readily apparent 1 hr after treatment with biliverdin or bilirubin but required >/=2 hr with hemin." "These data indicate that bilirubin induces Cyp1a1 gene transcription through direct interaction with the AHR. In contrast, hemin **and biliverdin seem to induce Cyp1a1 indirectly by serving as precursors to the endogenous formation of bilirubin via normal heme metabolism pathways. This is the first direct demonstration that the endogenous heme metabolite bilirubin can directly regulate Cyp1a1 gene expression and enzymatic activity in an AHR-dependent manner."**

J Biochem (Tokyo) 1997 Jun;121(6):1162-8 **Possible implications of the induction of human heme oxygenase-1 by nitric oxide donors.** Takahashi K, Hara E, Ogawa K, Kimura D, Fujita H, Shibahara S To explore the involvement of nitric oxide (NO) in the induction of heme oxygenase-1, an essential enzyme in heme catabolism, we studied the effects of NO donors on the expression of heme oxygenase-1 **mRNA in HeLa human cervical cancer cells. Treatment with each of three NO donors, sodium nitroprusside, 3-morpholinosydnonimine, and S-nitroso-L-glutathione, caused noticeable increases in the expression levels of heme oxygenase- mRNA, but** not heme oxygenase-2 mRNA. On the other hand, nitrite or 8-bromo cGMP exerted no noticeable effect on the levels of heme oxygenase-1 mRNA. We showed that sodium nitroprusside also increased the **levels of heme oxygenase-1 protein.** The sodium nitroprusside-mediated increase in heme oxygenase-1 mRNA levels was abolished by treatment with actinomycin D. The expression levels of heme oxygenase-1 mRNA were also **increased by NO donors in human melanoma and neuroblastoma cell lines.** Thus, the observed induction of heme oxygenase-1 may represent an important response to NO or NO-related **oxidative stress.** The half lives of heme oxygenase-1 and heme oxygenase-2 mRNAs were estimated to be about 3.2 h and more than 5 h, respectively.

Ann N Y Acad Sci 1998 May 1;840:249-61 **Acute and subacute effects of endotoxin on hypothalamic gaseous neuromodulators.** Kostoglou-Athanassiou I, Jacobs RA,

Satta MA, Dahia PL, Costa A, Navarra P, Chew SL, Forsling ML, Grossman AB.

Biokhimiia 1987 Sep;52(9):1501-11 **[Activation of lipolysis and ketogenesis in tumor-bearing animals as a reflection of chronic stress states].** [Article in Russian] Chekulaev VA, Shelepov VP, Pasha-zade GR, Shapot VS In order to elucidate the peculiarities of brain metabolism in tumour-bearing organisms, the arterio-venous (A-V) content of glucose, acetoacetate (Ac-Ac), beta-hydroxybutyrate (beta-HB) and non-esterified fatty acids (NEFA) in growing Zajdela ascite hepatoma (ZAH) and solid hepatoma 27 (H-27) was compared. Analysis of metabolic patterns of healthy, starving and fed recipients (ZAH and H-27) revealed the inadequacy of the concepts on anorexia as being the cause of carbohydrate-lipid metabolic disturbances. In tumour-bearing organisms **lipolysis and ketogenesis reflect the tumour-induced chronic stress.** Absorption of beta-HB and release of Ac-Ac by brain were observed at all stages of malignant growth. **This is probably due to a partial switch-over of brain metabolism to non-carbohydrate energy sources.** Besides, certain stages of tumour growth are associated with **active assimilation of NEFA by brain.** A correlation between the A-V difference with respect to glucose and Ac-Ac as well as between the glucose and NEFA contents was established. It was assumed that the A-V difference in glucose is the main regulator of ketone body metabolism.

Arkh Patol 1987;49(6):10-8 **[Combination of immunodepression and disorders in nucleic acid metabolism of lymphoid tissue as a manifestation of a paraneoplastic syndrome].** [Article in Russian] Potapova GI, Shapot VS Several physiological, biochemical, and molecular biological approaches to the study of factors determining immunodepression in tumor-bearing animals are considered. Cancer cells release substances of nucleic and peptide nature that suppress the functional activity of macrophages and lymphocytes and stimulate cell proliferation in organs and tissues of the host. Suppressor T cells capable of inhibiting the function of helper T cells and impairing the differentiation of killer T cells are activated. The suppression **of T- and B-cell-mediated immunity in the tumor host involves disturbances of nucleic acid metabolism in those cells as well as hypersecretion of glucocorticoids.** The impairments of lymphocyte proliferation and differentiation that result in reduced immune responsiveness are attributable to drastic alterations in the metabolism of purine and pyrimidine nucleotides and to the damage sustained by the lymphocyte's DNA.

Eksp Onkol 1987;9(6):62-7 **[Relation between disorders of glucose metabolism, secretion of somatotropic hormone, thyroxine, thyrotropin and hematocrit indices in rats with transplanted hepatomas].** [Article in Russian] Shelepov VP, Pasha-zade GR, Chekulaev VA, Shapot VS **The levels of growth hormone (GH) in the blood of rats with ascite Zajdela hepatoma and hepatoma 27 (H-27) are shown to increase during the tumour growth. Stimulation of the GH secretion is a result of the hypoglycaemic stress.** An increase in the blood GH secretion is also observed in the fasting rats. To reveal the **predominance of catabolic GH effects over the anabolic ones** in the tumour host determination of the molar insulin/GH ratio in the blood is suggested. A direct correlation is found between reduction of this index, glycaemia and the content of liver glycogen. A short-term induced hyperglycaemia evokes a paradoxical reaction in terms of GH secretion. In contrast to control fasting rats, in tumour-bearing animals no **correlation between thyrotropin and thyroxine blood concentration could be observed. Anaemia increasing progressively in the course of the tumour growth may be the cause of the above phenomenon.**

J Neuroendocrinol 1998 Oct;10(10):793-802 Influence of carbon monoxide, and its interaction with nitric oxide, on the adrenocorticotropin hormone response of the normal rat to a physico-emotional stress. Turnbull AV, Kim CK, Lee S, Rivier CL "We determined whether the gas carbon monoxide (CO) altered the adrenocorticotropin hormone (ACTH) response to mild inescapable electrofootshocks, and whether it interacted with nitric oxide (NO). Peripheral injection of the NO synthase (NOS) inhibitor Nomeganitro-L-arginine-methylester (L-NAME), a compound which readily crosses the blood-brain barrier, produced the expected blunting of the ACTH response to the shocks. This effect was mimicked by other arginine analogues such as L-nitroarginine (L-NNA) and NG-methyl-L-arginine (NMMA). The subcutaneous (s.c.) administration of the heme oxygenase (HO) blockers tin mesoporphyrin (SnMP) or tin protoporphyrin (SnPP) significantly decreased brain HO levels, indicating that both compounds had penetrated the brain." "SnMP and SnPP both decreased shock-induced ACTH release, though the magnitude of this effect was slightly less than that of L-NAME. The influence of SnPP was further augmented in rats with concomitant blockade of NO formation, which suggests that both NO and CO are necessary for the full response of this axis to electrofootshocks. Finally, the ability of SnPP to significantly blunt the expression of the mRNA for the immediate early gene NGFI-B in the paraventricular nucleus (PVN) of rats exposed to shocks, indicates that the influence of CO was exerted on hypothalamic neuronal activity. Collectively, our results show that NO and CO exert a **stimulatory effect on the HPA axis response to mild electrofootshocks, and that at least part of this influence takes place on hypothalamic neurons and/or their afferents."**

J Neurochem 1994 Sep;63(3):953-62 **Corticosterone regulates heme oxygenase-2 and NO synthase transcription and protein expression in rat brain.** Weber CM, Eke BC, Maines MD Heme oxygenase (HO)-1 and -2 produce carbon monoxide, which is suspected, as is nitric oxide (NO), to function as a neuronal messenger. We report on glucocorticoid-mediated modulation of HO-2 and NO synthase expression in brain and the differential response of the two proteins to corticosterone in different brain regions. Corticosterone treatment (40 mg/kg, 20 days) had opposing effects on HO-2 and NO synthase transcript levels:

increasing the 1.3- and 1.9-kb HO-2 mRNAs and decreasing that of the brain-specific 10.5-kb NO synthase. Corticosterone did not uniformly affect HO-2 protein expression in all regions, but appeared to cause a universal reduction in NO synthase, e.g., HO-2 was decreased in hippocampus (CA1 and dentate gyrus), but not in cerebellum. In contrast, NADPH diaphorase staining was reduced in hippocampus and in molecular and granule layers of cerebellum (not detected in Purkinje cells). **Striking deficits in neuronal morphology and number of diaphorase-staining neurons were observed in the lateral tegmental area, paraventricular nucleus, and frontal cortex; HO-2 expression was only selectively affected. In cerebellum, activity of NO synthase, but not that of HO, was reduced. Consistent with the possibility that carbon monoxide can generate cyclic GMP, the change in cyclic GMP level did not mirror the decrease in NO synthase. We suggest that glucocorticoid-mediated deficits in hippocampal functions may reflect their negative effect on messenger-generating systems.**

Acta Oncol 1995;34(3):329-34 **Relationship between tumour oxygenation, bioenergetic status and radiobiological hypoxia in an experimental model.** Nordsmark M, Grau C, Horsman MR, Jorgensen HS, Overgaard J. "Tumour oxygenation and bioenergetic status were measured in the same tumour and these results related to radiobiological hypoxia. A C3H mouse mammary carcinoma grown in the feet of CDF1 mice was used." "In conclusion, oxygen electrode measurements were sensitive to changes in tumour hypoxia whereas **the bioenergetic status alone seemed to be a less precise measure of hypoxia** in this tumour model. Furthermore, the present study demonstrated that tumour cells in vivo can actually maintain the bioenergetic status during a period of severe hypoxia."

Mutat Res 1998 May 25;400(1-2):439-46 **Mutagenesis induced by the tumor microenvironment.** Yuan J, Glazer PM **"Genomic instability is a commonly observed feature of tumors. Most investigations addressing the mechanism of tumor progression have focused on the genetic factors that may play a role. Growing evidence now suggests that, in addition to these endogenous factors, the exogenous environment within solid tumors may by itself be mutagenic and constitute a significant source of genetic instability. The tumor microenvironment is characterized by regions of fluctuating hypoxia, low pH, and nutrient** deprivation. Each of these microenvironmental factors has been shown to cause severe disturbance in cell metabolism and physiology. Both in vivo and in vitro data demonstrate that exposure of tumor cells to **adverse conditions can directly cause mutations, contributing to genetic instability. In this review, we will reexamine the current body of evidence on the role of the tumor microenvironment in inducing mutagenesis and consequent tumor progression."**

Lakartidningen 1995 May 24;92(21):2197-2198 **[Estrogen treatment caused acute attacks of porphyria].** [Article in Swedish] Wetterberg L, Olsson MB, Alm-Agvald I. Two female patients with acute intermittent porphyria, who received oestrogen skin pads as supplementary treatment for postmenopausal discomfort, developed severe psychiatric disorders with persistent confusion, aggression and paranoid reactions. Some decades earlier they had reacted with symptoms of acute porphyria following oral contraceptive usage. There is well documented evidence of the advisability of restrictiveness in the use of oestrogens in conjunction with acute porphyria, particularly in cases of patients with a history of hormone-related symptoms of acute porphyria. The putative mechanisms by means of which oestrogens may exert effects on neurotransmitters and peptides are discussed in the article. The authors would be grateful to hear from colleagues abroad who have treated patients with similar symptoms following postmenopausal treatment with oestrogens.

J Am Acad Dermatol 1994 Aug;31(2 Pt 2):390-392 **Porphyria cutanea tarda: pregnancy versus estrogen effect.** Urbanek RW, Cohen DJ Department of Medicine, Staten Island University Hospital, NY 10305. We describe the worsening of porphyria cutanea tarda in a young woman while she was taking oral contraceptives. However, she did not have an exacerbation during two pregnancies. We conclude that estrogens produced during pregnancy do not exert the same effect as orally administered medications that contain estrogen. The pronounced effect of oral ethinyl estradiol on the liver may be attributed to its first-pass effect on that organ.

Int J Radiat Oncol Biol Phys 1998 Nov 1;42(4):849-53 **The comparative effects of the NOS inhibitor, Nomega-nitro-L-arginine, and the haemoxygenase inhibitor, zinc protoporphyrin IX, on tumour blood flow.** Tozer GM, Prise VE, Motterlini R, Poole BA, Wilson J, Chaplin DJ.

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Ray Peat's Newsletter

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Progesterone and ideas of "balance" in "hormone replacement therapy": The importance of inhibition

Because I came to progesterone research after involvement in other biological issues such as the study of the effects of nuclear fallout and ionizing radiation on the brain, rather than as a physician, I had no commitment to any of the ideas which had grown up with the pharmaceutical industry, and that have become so basic to the professions' understanding of the actions of drugs and hormones. For example, *receptors* are supposed to be part of our genetic constitution, making us able to respond to drugs, poisons, hormones, infections, allergens, nervous stimuli, odors, etc. A substance, by binding to its receptor, sets in motion a biological response. With stimuli such as odors and adrenalin, there is a certain logic to the situation—with prolonged stimulation, fatigue sets in, we adapt to a certain level of stimulation, and it then takes a larger amount of the stimulus to produce a response. The receptors are "desensitized."

But if a stimulus evoked, or increased the quantity of, its own receptor, *increasing* the tissue's sensitivity, there would be a tendency for things to get out of control. What could be the biological meaning of such a situation?

Imagine applying this principle to various kinds of receptors—any odor would tend to increase until it became overpowering, the heart would be accelerated by smaller and smaller stimuli, or would require stronger and stronger impulses from the vagal nerve to restrain it. **Allergy represents what happens when a stimulus creates increased sensitivity to itself;** autoimmunity and lymphoma could represent similar processes of positive-feedback, increasing responses to a given level of stimulation. Excitotoxicity, epilepsy, movement disorders, and mania are other examples of what happens when negative (inhibitory) feedback fails. (Estrogen's interactions with other excitatory processes, such as allergy, will be considered in other articles; see Kalogeromitros, et al., 1995; Ahmed, et al., 1989.)

Estrogen's action on many tissues increases the tissue's ability to bind estrogen; estrogen induces its own "receptor," in a self-stimulating, self-destabilizing process. This is unlike the behavior of other "receptors," such as the adrenalin receptor, which is inactivated by increased exposure to adrenalin. This unusual interaction between tissue and hormone requires careful examination.

For example, estrogen's immediate effect on a responsive tissue is to cause it to take up water, and to increase its ratio of sodium to potassium; these changes lead to depolarization-activation of nerve, muscle, and some glandular cells, and of initiation of growth and cell division in other cell types. If the stimulation to growth process continued unchecked, or even accelerated, it's obvious that form and proportion and organization would quickly be lost. Similarly with the other forms of stimulatiion—activated responses must not continue beyond the organism's need for them.

Estrogenic stimulation, like an allergic reaction, would tend to increase progressively, if it weren't for the antiestrogens. The antiinflammatory effect of the glucocorticoids on an allergic reaction, preventing anaphylactic shock, are analogous to the effects of the antiestrogens, blocking estrogenic stimulation. The analogy is especially interesting, when we consider that Selye characterized estrogen's effect as similar to the shock phase of the stress reaction, and that antihistamines are generally

Hirsutisme = ↑ actw ↑ stimu surre
l'efficacité de la réponse (2 inhibition) face à la stimu est très importante

antiestrogenic, and antiestrogens are generally antihistaminic.

Since the actual levels of estrogen increase (Musey, et al., 1987; also see Rodriguez, et al., 1993 and O'Rourke, et al., 1996) during a woman's reproductive years, and then often act almost unopposed during a time around menopause (Nencioni and Polvani, 1985), and tend to increase progressively in aging men, and in both sexes during stress, we need to know what our protective systems are, for interrupting estrogen's excitatory actions on a great variety of tissues.

(1) One of progesterone's effects is to degrade and eliminate estrogen receptors (Brown and MacLusky, 1994; Medlock, et al., 1994; Okulicz, et al., 1993; Selcer and Leavitt, 1988). This is clearly an antiestrogenic action, and many people like to say the opposite, that progesterone induces estrogen receptors, simply because the idea suits their their doctrines of synergy, balance, and more basic ideas of genetic constitution, the nature of gender, etc. But the facts are so clear that they will have to look elsewhere for something to support their orientation.

(2) Recently it has been found that estrogen receptors are degraded by proteasomes (Nawaz, et al., 1999; Alarid, et al., 1999). This could relate to the fact that unsaturated fatty acids promote the retention of estrogen in the cell, since unsaturated fatty acids often inhibit proteolytic enzymes.

(3) By reducing the cell's ability to bind estrogen, progesterone acts as an "estrogen repellant." But

(4) it also activates enzymes* which physically/chemically detoxify estrogen, converting it to a water-soluble sulfated form, in which it tends to be expelled from cells and to be excreted in the urine.

(5) On the systemic level, progesterone helps to activate the liver's detoxifying systems, in which other types of enzymes modify estrogen, reducing its activity and preparing it for excretion, in both the bile and the urine.

One way of looking at progesterone is that it is an antiestrogen. The estrogen industry doesn't like that concept, and prefers to think of progesterone as an estrogen *synergist*. But if its effect is to interrupt estrogen's excitatory actions, and to eliminate estrogen from the tissues, it is no more "synergic" with estrogen than the inhibitory impulses of the vagus nerve are synergic with the excitatory adrenergic influences. The FDA, in its service to industry, has classified progesterone as a "progestin," defining the category only in terms of an effect on the uterus. No other pseudo-scientific concept exceeds this in its harmful consequences.

But to describe progesterone as an antiestrogen is meaningful only to the extent that we understand the nature of estrogenic stimulation.

Estrogen, as an easy derivative of testosterone, is deeply involved in the establishment of masculine features; even in mature women, estrogen excess (progesterone deficiency) can produce hirsutism and other masculine traits when it overstimulates the adrenal glands. As a goad (the term estrogen is based on *estrus*, gadfly, intense stimulus, goad), estrogen initiates activity in cells and systems; depending on the organism's resources, that stimulus will be restrained before it gets out of control.

Does the specific outcome of stimulation take its direction from estrogen, or rather from the ways in which estrogen is neutralized and detoxified? There are many antiestrogenic systems (e.g., thyroid, progesterone, testosterone, sulfation, methylation, glucuronidation, antiinflammatory factors, etc.) and the varied, specific nature of the organism's response to stimulation is probably sufficient to account for the different outcomes, such as masculinity or feminity, tumefaction or growth, alertness or mania.

How specific is estrogenic stimulation itself? Asphyxia, radiation injury, vitamin deficiencies, and other harmful stimuli, closely mimic the estrogenic excitation/shock response. (Boling, et al., 1939;Mandl and Zuckerman, 1956; Biskind, 1946.) Estrogenic activation, with the uptake of water and the loss of potassium (relative to intracellular sodium), is probably the simplest reaction a cell is capable of, and any specificity that can be found in the process is the result of pre-existing cellular conditions, or of defensive reactions of the organism. **Depending on its place in the life of an individual, estrogen can either masculinize or feminize, produce breasts or whiskers.**

Estro ↑ = ↑ H2o ↑ Na+ Intracell ↓ K+ intracell

Allergic Shock = ↑ histamine ↑ glucocor ↑ mucus

Hydratation cellularge important

The similarity of radiation injury to estrogenic stimulation has led to studies showing some radiation protection from progesterone; similar protective actions of progesterone can be seen for other types of injury. Thyroid, and other antiestrogens, also have a wide spectrum of protective actions, against radiation, asphyxia, carcinogens, etc.

I think the only way to approach the *general nature* of cellular excitation is to see it in terms of the basic properties of the living material. Only something as general and basic as the cell's state of hydration, its "wetness," can account for the coherent way in which cells are activated, with related processes happening at all levels, from chromosomes, to mitochondria and enzymes, the structural protein meshwork of the cytoskeleton, and sensory functions.

Cells use something like metaphor or analogy (as previously discussed in relation to J. Cairns' work, and e.g., in observations such as those of Smith, et al., 1990) to achieve coordination over long distances, and a medium of coordination and cooperation is needed; cell water, with its rich structural potential, provides that medium.

What do these perspectives imply for medical practice?

First, that the issue of "estrogen defiiciency" must be weighed very carefully. 35 years ago, men were given estrogen "to protect them from heart attacks," and the treatment increased the incidence of heart problems; several new campaigns are underway to use estrogens to protect both men and women from heart attacks. The arguments for "cardioprotective" actions of estrogen are based on very peculiarly chosen "indicators," excluding from consideration estrogen's contributory role in diabetes, elevation of free fatty acids and triglycerides, in the tendency to clot, synergism with adrenalin in spasticity of blood vessels, and other conditions relevant to heart disease. Similar campaigns, contrary to facts, are being developed in "brain protection," and other imaginary benefits of estrogen. Consistently, it has been found that the "positive results" found among women who take estrogen aren't scientifically valid, since the groups were selected in such a way that the women who took estrogen were healthier to begin with than the women who didn't take estrogen.

In the light of such imagined protective effects of estrogen, supplements are being recommended, either without any measurement of estrogen, or on the basis of finding a "low level" of estrogen, without taking any of the opposing or balancing factors into account. The idea of "estrogen deficiency," like that of "estrogen's protective action,". is completely without scientific foundation.

Any idea of balance suggests that there could be an imbalance in either direction. The harm done by unopposed estrogenic stimulation is clear. Does an excess of progesterone occur, and if it does, is it harmful? Animal experiments, in particular, have made it clear that, at a certain level, and in the absence of interfering factors, progesterone's sedative action can reach the level of deep anesthesia. When Selye's lab technicians discovered this effect, they thought they had killed the animals, because of the animals' complete relaxation and unresponsiveness. There have been no publications of a similar effect in humans (largely because of editorial policies, rather than from a lack of experimental evidence), but if there were, the anesthetized condition would have to be characterized as being harmful only in the behavioral sense, since tissues aren't harmed. When tumors of the corpus luteum produce very large amounts of progesterone, anesthesia has never been a recognized consequence of such massive production of progesterone. Many years of animal and human study indicate that the health of the mother during pregnancy, and of the offspring, directly correspond to the amount of progesterone present. (Excess estrogen during pregnancy leads to fetal death, retardation, or subsequent health problems including breast cancer.)

Progesterone production increases tremendously during pregnancy, reaching hundreds of milligrams per day in late pregnancy, so it is hard to think of it in terms of a "hormone," as traditionally defined. Like serum albumin, I think progesterone should be thought of primarily as a physical/chemical protective substance. But, unlike albumin, its protective properties just seem

to increase with concentration, right up to the absorptive limits of the cells. (The biological protection, however, at the upper extreme, includes sedation and anesthesia, and isn't compatible with ordinary function, and so, outside of the context of pregnancy (in which sedation and anesthesia are appropriate), these can be thought of as "side effects." Since they are part of progesterone's intrinsic function, though, the idea of "side effect" has to be understood as "collateral to the intended pharmacological effect." I think the idea of "side effect" connotes a doctrine of "one substance-one effect," something the drug industry promotes.)

Progesterone's functions include antitoxic or catatoxic effects, antiswelling and antiinflammatory effects, antiglucocorticoid and antiprostaglandin effects. When it alleviates a problem, that doesn't mean that the problem was caused by a progesterone deficiency. About 30 years ago, I proposed that biological energy, differentiation, and respiratory function are integrated in such a way that certain things stabilize/increase them, or destabilize/weaken them. Radiation, anoxia, and aging cause many coherent and systematic changes in function, and some of the things that have been classified as hormones or nutrients produce similar changes. Estrogen, I suggested, was produced to take advantage of something very basic in the nature of life, to promote reparative or regenerative functions. Like radiation, hypoxia, and a variety of stressors and nutritional imbalances, estrogen causes cells to take up water, and to shift away from respiratory metabolism, going into the mitotic state.

Besides being an antiestrogen, progesterone is a neurosteroid, an antiexcitotoxin, an inhibitory modulator. But these effects in the nervous system have their parallels in the immune system, where it modulates the actions of many cells, protecting the thymus, restraining mast cell degranulation, inhibiting the shock reaction. It is an antitoxin, stabilizing cell structure and function. In the mitochondria, it preserves or restores respiratory efficiency. In.the circulatory system, it regulates heart action and vascular tone, preventing venous pooling of the blood and orthostatic hypotension, helping to keep the pulse pressure in the low range indicating efficient circulation.

Therapeutically, we can think in terms of what the organism is doing in response to its challenges, and support those processes of restoration, adaptation, inhibition, and reconstruction.

Because excitation or stress is a simple thing--it is any disturbance of the living state's quiescence--radiation damage, asphyxia, nutritional deficiencies, various poisons, carcinogens, and irritants can imitate the actions of estrogen. Or, looking at estrogen's meaning in evolution, we could say that estrogen imitates the natural menaces that life confronts, so that the processes of regeneration can be managed and integrated into the life plans of the organisms.

This means that antiestrogenic strategies are appropriate under a great variety of conditions. Whatever the challenge, a successful response will restore the organism to a new, high energy state of readiness.

Estrogen's excitatory function, acting briefly, is an integral part of the organism's preparation for reproduction, and it is involved, in an analogous way, in the response to injury, where its local release stimulates cell division. If stimulation has such generalized properties that noxious events and a natural hormone produce similar reactions, what kind of role does stimulation play elsewhere in the organism?

The interaction of energy and structure in the cell means that an energy deficit becomes excitatory. In the case of nutrition, this has been worked out in relatively great detail. Hypoglycemia, for example, causes a graded, progressive excitation, that first makes food appetizing, and then, if the excitation is continued and intensified, there is a more generalized arousal, and the image of the desired food becomes more generalized. Need and arousal mobilize various functional systems to satisfy the need. Pavlov, working on these issues, knew that it was essential to answer the question, "what stimulates the activities that we consider uniquely human?" The exploratory reflex is activated by novelty, by anything which isn't understood. The need/desire for freedom and understanding has the same basic pattern as

the other needs, and it has apparently evolved by differentiation from the basic sensitivity of the living material.

The relatively mild stimulation of novelty, when combined with meeting basic needs and preventing irrelevant, stressful stimulation, can be therapeutic. For example, in a digestive disturbance, therapeutic stimulation might be achieved by something as mild as beef broth, acting by intrinsic (unconditional) chemical processes, or by some simple alteration in the way the food is prepared, or a change in the mealtime atmosphere. The therapeutic effect of laughter, which is produced by surprise, can be seen in terms of a basic organismic process of organizing resources, creatively adapting to produce a new state of readiness.

In outline, a benign stimulation is one which can be met with adequate energy, with good humor, and with an adequate amount of progesterone and related chemical resources.

All of the information that has accumulated about estrogen in the last century leads to the view that it is the organism's means of producing a **momentary and localized imbalance,** goading cells into activity.

An important factor in the integration of this momentary imbalance into the life of the organism is the manner in which destabilizing excitation and the restoration of stability, e.g., estrogen and progesterone production, relate to each other. Estrogen stimulates the formation of progesterone, and progesterone lowers the concentration of estrogen. (Liu, et al., 1997)

Whether we consider pregnancy, or bone metabolism, or the health of the brain or the circulatory system, no situation has been identified in which the "balance of estrogen and progesterone" can be improved by the use of estrogen supplementation. But there is a tremendous amount of information showing that reproduction and the health of bones, brain, and circulatory system, and many other functions, can be improved by antiestrogenic approaches. The pharmaceutical industry is trying to exploit this information, by reclassifying their *antiestrogenic* drugs as "designer estrogens." But the body already has its proper array of antiestrogenic strategies, which can be supported in many safe and economical ways.

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Am J Epidemiol 1996 May 15;143(10):971-8. **Prior to use of estrogen replacement therapy, are users healthier than nonusers?** Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P Department of Psychiatry, University of Pittsburgh School of Medicine. **"Women who elect to use ERT have a better cardiovascular risk factor profile prior to the use of ERT than do women who subsequently do not use this treatment during the menopause, which supports the hypothesis that part of the apparent benefit associated with the use of ERT is due to preexisting characteristics of women who use ERT."**

Am Heart J 1998 Jul;136(1):115-24 Comparison of the Heart and Estrogen/Progestin Replacement Study (HERS) cohort with women with coronary disease from the National Health and Nutrition Examination Survey III (NHANES III). Herrington DM, Fong J, Sempos CT, Black DM, Schrott HG, Rautaharju P, Bachorik PS, Blumenthal R, Khan S, Wenger NK Internal Medicine/Cardiology and Public Health Sciences, Wake Forest University School of Medicine. **"There were fewer current smokers in HERS (13%) than in the NHANES cohort (21.7%, p = 0.05). Similarly, a history of hypertension was less prevalent in HERS (58.6%) than in the NHANES cohort (69.3%, p = 0.03). Women with fasting triglyceride levels >3.39 mmol/L or fasting glucose levels >16.6 mmol/L were excluded from HERS, resulting in fewer diabetics (22.9% vs 29.5%, p = 0.26) and lower serum triglyceride levels (1.88 mmol/L vs 2.25 mmol/L, p = 0.19) in HERS versus the NHANES cohort."**

Mol Endocrinol 1999 Sep;13(9):1522-34. **Proteasome-mediated proteolysis of estrogen receptor: a novel component in autologous down-regulation.** Alarid ET, Bakopoulos N, Solodin N The Department of

Physiology, University of Wisconsin-Madison. **"Regulation of estrogen receptor (ER) concentration is a key component in limiting estrogen responsiveness in target cells."** "Proteolytic regulation of ER by the **proteasome is not limited to pituitary lactotrope cells but is also operational in MCF-7 breast cancer cells,** suggesting that this may be a common regulatory pathway used by estrogen. These studies describe a **nongenomic action of estrogen that involves nuclear ER: rapid proteolysis of ER protein via a proteasome-mediated pathway."**

J Neuroendocrinol 1995 Feb;7(2):119-25 Regulation of estrogen receptor and progesterone receptor messenger ribonucleic acid by estrogen in the brain of the whiptail lizard (Cnemidophorus uniparens). Young LJ, Nag PK, Crews D. "First we determined a dosage of 17 beta-estradiol 3-benzoate (0.5 micrograms) which reliably induced receptive behavior in ovariectomized C. uniparens. Then using in situ hybridization, we examined the effects of that dosage on the expression of estrogen receptor and progesterone receptor mRNA in the brain 24 h after injection. Estrogen treatment resulted in a **significant up-regulation of estrogen receptor mRNA expression in the ventromedial nucleus of the hypothalamus and torus semicircularis,** down-regulation of estrogen receptor mRNA expression in the lateral septum, and no change in the periventricular nuclei of the hypothalamus, the periventricular nucleus of the preoptic area, and the dorsal hypothalamus. **The same dosage resulted in increased progesterone receptor mRNA expression in the ventromedial nucleus of the hypothalamus and the periventricular nucleus of the preoptic area;** no significant changes in progesterone receptor mRNA expression were observed in the periventricular nuclei of the hypothalamus or the torus semicircularis, although the differences in progesterone receptor expression in the torus semicircularis approached statistical significance."

Mol Cell Neurosci 1994 Jun;5(3):283-90. **Progesterone modulation of estrogen receptors in microdissected regions of the rat hypothalamus.** Brown TJ, MacLusky NJ **"One mechanism whereby progesterone opposes the regulatory actions of estrogen in the brain may include the down-regulation of estrogen receptors. A previous study has shown a small decrease in estrogen binding in the combined preoptic area-hypothalamic area in response to progesterone treatment."** "A significant decrease **in estrogen binding was found in the ventromedial nucleus of the female but not the male. A significant effect of progesterone treatment was found in the periventricular preoptic area of the male."**

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Biol Reprod 1993 Jul;49(1):24-32 Progesterone regulation of endometrial estrogen receptor and cell proliferation during the late proliferative and secretory phase in artificial menstrual cycles in the rhesus monkey. Okulicz WC, Balsamo M, Tast J. **"Progesterone (P) down-regulation of uterine estradiol (E) receptor (ER) appears to be a general mechanism by which P modulates E action in the uterus."**

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Endocrinology 1989 Jul;125(1):392-9 Down-regulation of estrogen receptors by androgens in the ZR-75-1 human breast cancer cell line. Poulin R, Simard J, Labrie C, Petitclerc L, Dumont M, Lagace L, Labrie F. "Much clinical evidence indicates that androgens have beneficial effects in the treatment of breast cancer in women." "Similar inhibitory effects are observed on the levels of ER messenger RNA (mRNA) measured by ribonuclease protection assay."

Gen Comp Endocrinol 1988 Dec;72(3):443-52. **Progesterone down-regulation of nuclear estrogen receptor: a fundamental mechanism in birds and mammals.** Selcer KW, Leavitt WW.. "Progesterone is known to selectively down-regulate nuclear estrogen receptor (Re) in the mammalian uterus, and this process is functionally related to embryo retention." "We investigated the regulation of Re by progesterone in a mammalian model (proestrous hamster uterus) and an avian model (DES-primed chick oviduct), under the same assay conditions, in an effort to compare progesterone action in viviparous and oviparous species." "Progesterone treatment reduced nuclear Re levels in both the hamster uterus and chick oviduct to about 50% of control levels." "These data indicate that progesterone rapidly and selectively down-regulates the nuclear form of Re in the chick oviduct as in the hamster uterus. Thus, the regulation of Re by progesterone appears to be similar in the mammalian uterus and the

chick oviduct, despite the basic differences in reproductive strategy between birds and mammals."

Adv Exp Med Biol 1987;230:49-78. **Progesterone-modulation of estrogen action: rapid down regulation of nuclear acceptor sites for the estrogen receptor.** Leavitt WW, Cobb AD, Takeda A. "Our previous studies demonstrated that progesterone down regulates the occupied form of nuclear estrogen receptor (Re)." ". . . we discovered that progestins stimulate the turnover of nuclear Re within 3 h of treatment, and Re synthesis is suppressed subsequently. Thus, the primary site of progestin action in down-regulating Re is the stimulation of nuclear Re turnover followed by the inhibition of Re replenishment. A major breakthrough in our understanding of how progestin controls Re turnover was made by studying nuclear acceptor sites for Re that were found to decrease markedly within 2 h of progestin treatment. These and other results indicate that progestin induces a factor called the Re regulatory factor (ReRF) which acts to block nuclear Re acceptor sites, and this in turn decreases nuclear Re retention on chromatin acceptor sites, leading to an enhanced turnover (or processing) of nuclear Re."

J Steroid Biochem 1986 Aug;25(2):219-24. **Temporal effects of progesterone domination on estrogen and oxytocin receptors in hamster uterus.** Takeda A, Leavitt WW. "The purpose of this study was to determine whether progesterone (P)-induced down regulation of estrogen receptors (Re) and oxytocin receptors (ROT) changes with the time of P exposure." "These results demonstrate that P can chronically down regulate nuclear Re and ROT. However, the control of cytosol Re varies with the time of P exposure, and cytosol Re levels become refractory to P domination by 16 days. The present observations indicate that the escape of cytosol Re from P control may be associated with the proliferation of one of more uterine cell populations such as glandular and luminal epithelial cells."

Endocrinology 1985 Mar;116(3):1079-84. **Hormonal regulation of myometrial estrogen, progesterone, and oxytocin receptors in the pregnant and pseudopregnant hamster.** Leavitt WW. "Comparison of Re and Rp levels with serum estradiol and progesterone titers revealed that receptor concentration was low when progesterone was elevated during pregnancy and pseudopregnancy. However, Re and Rp levels increased when progesterone levels dropped at the end of each condition. In comparing serum estradiol relative to progesterone at the end of pregnancy and pseudopregnancy, it was discovered that Re and Rp recovery occurred not only when the estradiol to progesterone ratio increased (pseudopregnancy) but also when the ratio did not change (pregnancy). **This suggested that serum progesterone was the primary determinant of receptor down-regulation, and this was confirmed** by comparing the receptor recovery response to estrogen and progesterone withdrawal in the decidualized hamster uterus. Total Re levels increased to the same extent after progesterone withdrawal whether or not serum estradiol was maintained. When serum estrogen was maintained at a steady state, nuclear Re (nRe) increased within 4 h of progesterone withdrawal, and estrogen-dependent protein responses (Rp and oxytocin receptor) were obtained within 8 h. Thus, progesterone-induced down-regulation of nRe and estrogen-dependent proteins is rapidly reversed upon removal of hormone. The recovery response of Re, Rp, and oxytocin receptor to progesterone withdrawal can be blocked by cycloheximide treatment at 4 h, suggesting that receptor **recovery involves protein synthesis. These results are consistent with the hypothesis that progesterone down-regulates the Re system by a selective action on nRe retention.**

Proc Natl Acad Sci U S A 1999 Mar 2;96(5):1858-62 Proteasome-dependent degradation of the human estrogen receptor. Nawaz Z, Lonard DM, Dennis AP, Smith CL, O'Malley BW Department of Cell Biology, Baylor College of Medicine. **"In eukaryotic cells, the ubiquitin-proteasome pathway is the major mechanism for the targeted degradation of proteins with short half-lives. The covalent attachment of ubiquitin to lysine residues of targeted proteins is a signal for the recognition and rapid degradation by the proteasome, a large multi-subunit protease."**. "The UBA and UBCs, which promote ER degradation in vitro, have no significant effect on human progesterone receptor and human thyroid hormone receptor beta proteins."

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Endocrine 1997 Apr;6(2):125-131. **Estrogen replacement in ovariectomized rats results in physiologically significant levels of circulating progesterone, and co-administration of progesterone markedly reduces the circulating estrogen.** Liu JW, Dawson DD, Peters CE, Baker MA, Walker AM Division of Biomedical Sciences, University of California, Riverside.. Estrogen and progesterone replacement in ovariectomized rats in an often-used experimental system for determination of the specific effects of these hormones. In this study, two different delivery systems and two different dosage levels of estrogen, progesterone or a combination of the two have been used. Estrogen and progesterone in the circulation have been measured in response to each treatment. **It is reported that estrogen treatment (237.2 +/- 49.2 pg/mL) results in physiologically significant levels of circulating progesterone (11.1 +/- 1.3 ng/mL).** Also, co-administration of progesterone (23.7 +/- 2.0 ng/mL) with estrogen decreases the level of estrogen over that seen with estrogen alone (96.7 +/- 19.2 pg/mL with progesterone vs 237.2 +/- 49.2 pg/mL without progesterone). Thus, contrary to expectations, **estrogen replacement therapy is not specific to estrogen** and some of the antagonistic effects of progesterone are the result of a decrease in circulating estrogen, and not a specific effect on a target tissue. Whereas the mechanism of these effects has not been determined, obvious artifactitous phenomena have been excluded as being their cause. These results could have

a major impact on the interpretation of past and future experiments of this kind.

J Hepatol 1994 Dec;21(6):1127-34 **The adverse influence of pregnancy upon sulphation: a clue to the pathogenesis of intrahepatic cholestasis of pregnancy?** Davies MH, Ngong JM, Yucesoy M, Acharya SK, Mills CO, Weaver JB, Waring RH, Elias E.. "Sulphation of oestrogens and monohydroxy bile acids is important in attenuating their cholestatic potential. Thus, impairment of sulphation could lead to retention of cholestatic compounds and precipitate intrahepatic cholestasis in susceptible individuals." "During in vivo studies utilising paracetamol as a metabolic probe, the proportion of paracetamol sulphate and sulphate: glucuronide ratio **were decreased in those with elevated oestrogens,** whether the rise in oestrogens was endogenous, in pregnancy (paracetamol sulphate $p < 0.05$; paracetamol sulphate:glucuronide ratio $p < 0.01$), or exogenous, with the contraceptive pill (paracetamol sulphate $p = 0.2$; paracetamol sulphate:glucuronide ratio $p < 0.001$)." "An imbalance of sulphation with glucuronidation provoked by high circulating oestrogen levels may be contributory in the pathogenesis of cholestasis of pregnancy."

Clin Exp Allergy 1995 May;25(5):461-6. **Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen.** Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I Department of Dermatology, University of Athens, A. Sygros Hospital, Greece. **"Results indicate a significant increase in weal-and-flare size to histamine, morphine, and parietaria on days 12-16 of the cycle, corresponding to ovulation and peak oestrogen levels.** This was observed in both atopic and non-atopic women. Differences in skin reactivity to histamine and morphine between the groups were not significant. Therefore, in women, the phase of the menstrual cycle is another factor that may influence skin-test results."

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Neuroscience 1993 Dec;57(3):861-71. **Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain myelin changes resembling early stages of demyelination.** Theoharides TC, Dimitriadou V, Letourneau R, Roznieckl JJ, Vliagoftis H, Boucher W Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111. **"Mast cells are known for their participation in immediate and, more recently, delayed hypersensitivity reactions. They have been found in the meninges and certain brain areas where they are strictly perivascular, in close apposition to neurons, and they are activated by direct nerve stimulation or by neuropeptides. Intracranial mast cells contain many vasoactive substances which can increase the permeability of the blood-brain barrier, proteolytic enzymes which can degrade myelin in vitro, as well as chemotactic molecules** which can attract inflammatory molecules in vivo. Connective tissue mast cells, with which intracranial mast cells share many characteristics, contain cytokines which can cause inflammation directly. **Multiple sclerosis is a human demyelinating disease of unknown etiology, with a high prevalence in women which results in penetration of blood-borne immune cells within the brain parenchyma and subsequent destruction of myelin. Here, we report that 17 beta-estradiol and myelin basic protein, a major suspected immunogen in multiple sclerosis, had a synergistic action on inducing mast cell secretion."**

Am J Obstet Gynecol 1987 Aug;157(2):312-317. **Age-related changes in the female hormonal environment during reproductive life.** Musey VC, Collins DC, Musey PI, Martino-Saltzman D, Preedy JR. "We studied the effects of age, independent of pregnancy, by comparing serum hormone levels in two groups of nulliparous, **premenopausal women aged 18 to 23 and 29 to 40 years. We found that increased age during reproductive life is accompanied by a significant rise in both basal and stimulated serum follicle-stimulating hormone levels. This was accompanied by an increase in the serum level of estradiol-17 beta and the urine** levels of estradiol-17 beta and 17 beta-estradiol-17-glucosiduronate. The serum level of estrone sulfate decreased with age. Serum and urine levels of other estrogens were unchanged."

T. Nencioni and F. Polvani, **"Rationale for the use of calcitonin in the prevention of post-menopausal osteoporosis,"** in Calcitonin, A. Pecile, editor, Elsevier Science Publ., 1985.

C. C. Johnston, et al., "Age-related bone loss," pages 91-100 in U. S. Barrel, editor, Osteoporosis II, Grune and Stratton, N. Y., 1979. **Johnston (1979) found that progesterone (but not estrone, estradiol, testosterone, or androstenedione) was significantly lower in those losing bone mass most rapidly.**

Ray Peat's Newsletter

The Questioner who sits so sly Shall never know how to Reply -- W. Blake

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Contexts for asthma

Asthma in children involves many of the biological processes that cause disability and degeneration in the process of aging, and since the incidence of asthma in children is increasing, it has serious implications for the whole population.

Increased exposure to estrogen (including prenatal exposure), increased consumption of unsaturated vegetable oils, use of food or drug additives including guar gum, carob, carrageenan, and sulfites, and the use of adrenergic ("beta-agonist") inhalant drugs have coincided with the increased death rates from asthma. Estrogen and unsaturated fats are clearly involved in producing the symptoms of asthma.

Living at high altitude decreases asthma prevalence and mortality. Exercise increases the incidence of asthma. These facts provide insight into the biochemical events of asthma.

The inflammatory-excitatory processes of asthma are parallel to those of depression, diabetes, premenstrual syndrome, arthritis, migraine, MS, SLE, multiple organ failure, aging, and death.

Protecting cellular energy and stability can prevent or alleviate asthma. Thyroid, progesterone, and carbon dioxide are therapeutically useful, but reducing exposure to polyunsaturated oils and estrogens should be the basic approach.

Medical theories of asthma give a better insight into the nature of medicine than into the nature of the asthmatic condition.

Evasion and misdirection were woven into the culture of pharmacology by the competition to sell products. The objective result has been something approaching genocide. The U.S. government has served as the agent of the drug industry, by outlawing generic remedies whenever a corporation sought to fill that niche with its newly patented substance. This practice is so fundamental that, when inquiry is made about getting FDA approval for a substance, the response is that you must first have a patent on the substance. On its face, this indicates that the agency is in a conspiracy against the public health, to permit only proprietary remedies to be used legally.

"Medical empiricism" traditionally referred to the use of remedies that worked, without trying to build a speculative or theoretical explanation for the way they worked or for the physiological nature of disease. "Scientific medicine" decided to call that approach quackery, and to build a theory of disease that would explain how remedies worked.

As it worked out, this meant that certain kinds of remedy were "validated" by certain types of theory. Commercial and cultural interests therefore fostered and promoted the theories that they found most profitable. Impressively "scientific" words were invoked to justify procedures that otherwise would have been considered barbaric. As microscopic technique developed, "humoral" theories of disease were replaced by cellular theories, and the cellular theories came to encompass the "genetic" theories of disease.

The specific, concrete nature of the "gene" concept became part of the "allopathic" tradition of medicine, in which a specific drug was appropriate for, "indicated" for, a specific symptom or disease. The holistic ideas associated with the homeopathic tradition disappeared from organized medicine in the United States. A fragmented and compartmentalized "health science" has been the result.

In the 17th century the term *diathesis* (constitutional predisposition) was coined to "explain" disease, and the term was replaced in the 20th century by the phrase "genetic cause."

Medical writers (and medical editors) are similar to politicians and college sophomores in their habitual use of the classical logical fallacies. When students use defective reasoning, the presumption is that they are confused, but when politicians and physicians argue fallaciously, the interpretation must include other possibilities.

If a certain theoretical explanation has become unnecessary and impossible, then a growing advocacy of that theory strongly implicates ulterior motives, and suggests corrupt influences.

Although there were individuals who believed that asthma was a "psychosomatic" disease or the result of an infection, the official medical position has been that it is a diathesis, a congenital disposition, a "genetic disease" (e.g., Castro, et al., 2001; Ishikawa and Tsujimoto, 2001). A genetic theory of disease is ideal for the drug business, since incurability guarantees continuing sales. Fads in asthma theory coincide with the availability of products. The defective genes have at various times been thought to produce excessive activity in the parasympathetic nervous system, or incontinent mast cells that leak histamine, or enzyme defects that produce too much Slow-Reactive-Substance or leukotriene, or weak adrenal glands, or genetic imbalances that affect the immune system in relatively simple or in more complex ways.

Sudden increases in asthma mortality in the 1960s and 1970s in various countries corresponded to increased use of certain synthetic adrenergic drugs (instead of adrenaline), called bronchodilators, as inhalants. The concept that they were "beta-agonists" was used to rationalize their use, even after animal experiments showed that they caused serious heart damage, and other harmful effects.

When the medical model of asthma shifted its emphasis from "smooth muscle spasm" to "inflammation," a shift that in the U.S. dates from a series of publications in the 1980s (Ackerman, 1989), there was the usual sense of accomplishment, as authors and medical professors spread the word about the latest inhaled steroid products, replacing the "synthetic adrenaline" inhalants that had been increasingly used during the years that asthma mortality had been rising so rapidly. That this change of medication was thirty years tardy wasn't mentioned. (G. Rona's group began publishing warnings in the early 1960s about the heart and vascular damage caused by adrenergic drugs such as isoproteronol.) Even as new medications came into use, there wasn't much change in medical knowledge about asthma. ***And even though there is evidence that oral glucocorticoids drastically reduce death from acute asthma (Abramson, et al., 2001), and that inhaled glucocorticoids have serious systemic side effects, the drug industry created another set of mystifications, claiming that inhaling certain synthetic steroids would act selectively upon the bronchial tubes and lungs.***

As far as I can tell, the only significant event that caused the change of emphasis in the medical model of asthma from "bronchial contraction" to "bronchial inflammation" was the promotion of steroids to replace the "bronchodilators." The description of the disease seems to change according to the drug that's being marketed.

Decades ago, the public accepted the medical doctrine that asthma, and allergies in general, were caused by genetic defects. With the tremendous increase in the death rate from asthma in recent decades (coinciding with similar increases in other supposedly "genetic" diseases), many people are de-emphasizing that theory, because an impossibly high rate of mutation would have been needed to create those "new genetic defects." However, few people are looking for a radically new theory of asthma.

Asthma would be a good place to make a fresh start in understanding chronic disease, and the first step has to be to abandon the unfounded and corrupt theory of genetic causation, and to begin the construction of a functional, environmental theory of its cause. If asthma can be understood functionally, there is a good chance that it can be prevented or cured.

Elite athletes are generally considered to have "good genes," and exercise is commonly said to promote good health, so a new orientation is

needed to accommodate the fact that **"elite" athletes, winter or summer athletes, including participants in the Olympics, have a high incidence of asthma--roughly three times higher than the general population.**

It turns out that exercise induces the signs and symptoms of asthma, not only in "asthmatics," but in normal people too.

Anaerobic exercise (getting out of breath) increases the release of, or activity of, a large variety of inflammatory mediators, beginning with lactic acid and interleukin-6 released from the exercised muscle itself, and including factors released from various cells in the blood, and hormones including estrogen, prolactin and sometimes TSH.

Figures from Mexico show that, in the states with high altitude, the prevalence of asthma is about ten times lower than the states that are close to sea level. Mountain therapy has been used for a long time to treat asthma and other chronic diseases, especially in Russia. In the United States, many publications have confirmed that high altitude alleviates asthma, but it is called "antigen avoidance therapy," despite evidence that shows improvement at high altitude even in the presence of the usual antigens, such as skin mites. All of the main mediators of inflammation decrease with increasing altitude.

The incidence of asthma in girls surpasses that in boys around puberty, and it is common for asthma to be worse premenstrually. The use of oral contraceptives often makes asthma worse. During pregnancy, asthma sometimes gets worse, sometimes better. At menopause, asthma is likely to get worse, and to appear in women who didn't previously suffer from asthma. The use of estrogen at menopause increases the incidence of asthma. Progesterone, and related hormones, alleviate asthma, and this probably accounts for the variable effects of pregnancy on asthma, since pregnancy can improve the ratio of progesterone to estrogen, but often, with poor nutrition, estrogen dominance is exacerbated by pregnancy. Estrogen exposure early in life can cause asthma later. The common use of DES during pregnancy in the 1950s was one of the factors that caused the increase of asthma in children in the 1960s.

Estrogen increases most of the mediators of inflammation, which are generally inhibited by progesterone. Estrogen also shifts many processes toward excitation, and it's often hard to distinguish the mediators of inflammation from the mediators of excitation. Free polyunsaturated fatty acids, for example, which are increased under the influence of estrogen (or exercise, diabetes, nighttime, aging, histamine, parasympathetic dominance, etc.), produce both inflammation and excitation. Associated with the processes of inflammation and excitation is the tendency of estrogen and other inflammatory mediators, such as nitric oxide and serotonin, to impair mitochondrial respiration. This effect on the cells' energy production is probably responsible for many of the things that occur in asthma, such as edema and smooth muscle contraction. Acute or chronic interference with mitochondrial respiration can produce a tremendous variety of symptoms, depending on the location, and the degree of the energy deprivation. Exercise, probably acting through some of the same mediators, also impairs mitochondrial respiration.

These factors that impair respiration tend to shift mitochondrial metabolism away from the oxidation of glucose and the production of carbon dioxide, to the oxidation of fats and the production of lactic acid.

The clear distinction between inflammation and excitation (and excitotoxicity) is largely an artifact of the drug industry's influence on medical theory.

The "spasmolytic" drugs that are intended to prevent contraction of the bronchioles can cause histamine release as well as increasing cortisol production, and they increase the level of free fatty acids as well as raising the blood sugar.

Simply shifting the cells' energy production away from the oxidation of glucose can produce excitability, inflammation, increased leakiness of blood vessels, changes in mucus, discharge of histamine and serotonin, hormonal changes, etc.

The doctrine of "preventing excessive weight gain" in pregnancy that dominated obstetrics-gynecology in the U.S. in the 1950s and 1960s probably contributed to the increased prevalence of asthma in the 'sixties and 'seventies, because

protein deficiency creates an inflammatory state, and a state of estrogen dominance. (Measurement of inflammatory proteins in the blood has been proposed as a way to confirm protein deficiency.)

One of the major "acute phase proteins," C-reactive protein, is defensive against bacteria and parasites, but it is suspected to contribute to tissue degeneration. When its presence is the result of exercise, estrogen, or malnutrition, then its association with asthma is likely to be causal, rather than coincidental.

Some of the "acute phase proteins" in the blood, that are associated with inflammation, rise progressively with aging, and are induced by estrogen. One of these stress-related proteins, serum amyloid P-component, is called the "female protein" in hamsters. This type of protein is implicated in atherosclerosis, Alzheimer's disease, heart attacks, and kidney disease.

The respiratory system is so intimately related to the circulatory system and other systems that the traditional classification of diseases can be misleading. Ordinarily, asthma is distinguished from bronchitis, emphysema, "Acute Respiratory Distress Syndrome" or "shock lung," pulmonary edema, surfactant deficiency, etc., as if each problem were clearly distinguishable by its intrinsic properties. Actually, there is considerable overlap, and the diagnostic distinction can depend on the patient's history and situation, rather than on the actual pathology. Even "High Altitude Pulmonary Edema" has important similarities to "bronchial asthma."

Even though breathing might be the immediate focus of attention, there is no health problem which isn't systemic. The old medical use of cathartics for asthma, epilepsy, headaches, arthritis, cancer, etc., was often based on good observation. Before medicine became "scientific," many cases of asthma and epilepsy were successfully treated with vermifuges, but now the role of parasites in these conditions is rarely considered.

The specific location of symptoms--bronchial asthma, migraine, hemorrhoids, sneezing, etc.--brought on by an allergen, such as worms or certain foods or constipation or intestinal gas, is influenced by nervous reflexes. Reflexes are exaggerated by stresses such as hypoglycemia or alkalosis. Experimenters, for example, found that inflating a balloon in the intestine of an anesthetized animal wouldn't produce any observable reactions when the blood sugar was normal, but when the blood sugar was lowered, bronchospasms or other localized reflexive reactions would be produced.

The allergic reaction produced by any substance is intensified by hypoglycemia, and weakened by elevated blood sugar. Decreasing or increasing sodium has a similar, but weaker, effect. (G. Jasmin, 1968)

Knowing something about the situation that preceded a breathing difficulty can be useful, especially as a guide to eliminating environmental problems, but the fact that so many conditions involve the same physiological/pathological components means that a few therapies can be rationally used for many "different diseases."

For example, **caffeine, thyroid, carbon dioxide, progesterone, and several other anti-serotonin drugs (e.g., tianeptine and ketanserin)** can be therapeutic for asthma, even when the specific causes aren't known.

Buteiko's recognition of the importance of carbon dioxide (and the avoidance of hyperventilation) in the prevention of asthma is validated by the fact that high altitude normally alleviates asthma, that carbon dioxide inhalation at high altitude relieves altitude sickness (indicating that altitude sickness, like asthma, is the result of relative hyperventilation), and that acetazolamide, which increases carbon dioxide retention and is used to prevent or treat high altitude sickness, also alleviates asthma.

Practically everything which is stressful will shift metabolism away from the adequate production of carbon dioxide. The use of oxygen supplementation to treat asthma or other respiratory difficulty without also supplementing carbon dioxide is unphysiological and dangerous.

In the 19th century in the U.S., cocaine was officially recognized as a therapy for asthma, and in South America coca is the traditional remedy for altitude sickness, but there has been very little scientific investigation of the therapeutic use of cocaine. It increases progesterone production and probably has antihistamine action. Atropine,

which is very similar in chemical structure to cocaine, was a standard drug for asthma until the synthetic antihistamines and bronchodilators displaced it. Although it's known mainly as an "anticholinergic," atropine can protect against the excessive liberation of free fatty acids that interferes with the use of glucose. Camphor, amantadine, procaine and other soothing anticholinergics or antihistamines had a similar fate, as far as asthma therapy is concerned. The antihistamine Benadryl is usually helpful in asthma and other inflammatory or spasmodic conditions.

Eucalyptus oil, containing cineole or eucalyptol, is a traditional remedy for asthma, that inhibits the products of unsaturated fatty acid metabolism and the cytokines most associated with asthma symptoms.

The uncontrolled release of many inflammatory and excitatory substances can be prevented by good nutrition, emphasizing adequate protein and magnesium intake, and the use of sugars and saturated fats, rather than starches and unsaturated fats. Vitamin E protects against the inflammatory actions of the unsaturated fats. The short-chain saturated fatty acids of coconut oil have been reported to have antihistamine actions. **The selection of proteins should minimize the amino acids tryptophan (which is the precursor of serotonin) and cysteine (which, like tryptophan, suppresses thyroid function), by including gelatin and fruits.** Gelatin is 22% glycine, which protects the lungs and other organs against toxins and inflammatory agents, and many fruits are also "deficient" in tryptophan and cysteine.

The overlapping effects of estrogen, polyunsaturated fats, exercise, serotonin, histamine, lactic acid, nighttime, and hyperventilation, tend to be cumulative and self-stimulating. Degenerative changes in tissues are accelerated by all of these stress mediators.

When these factors aren't corrected, the standard officially recognized treatments for asthma--despite the acute relief they can provide--will probably increase long-range morbidity and mortality. For short-term relief, combinations of safer materials can probably be found that will give the same immediate results, while helping to correct the underlying problems.

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J Endocrinol 1966 Jul;35(3):263-70. **The effects of treatment with gonadotrophins or with oestrogen on the thyroid gland of the immature rat.** Brown-Grant K. (Estrogen increases TSH.)

Am J Physiol Lung Cell Mol Physiol 2000 Aug;279(2):L390-8. **Dietary glycine blunts lung inflammatory cell influx following acute endotoxin.** Wheeler MD, Rose ML, Yamashima S, Enomoto N, Seabra V, Madren J, Thurman RG.

Chest 1990 Sep;98(3):651-5. **Acid-base disturbances in acute asthma.** Mountain RD, Heffner JE, Brackett NC Jr, Sahn SA. **"A simple respiratory alkalosis was the most common acid-base disturbance, occurring in 48 percent of the episodes."** " . . . the pathogenesis of **lactic acidosis** is multifactorial and includes contributions from lactate production by respiratory muscles, tissue hypoxia, and intracellular alkalosis."

West J Med 1988 Nov;149(5):551-4. **Long-term effects of exposure to diethylstilbestrol.** Wingard DL, Turiel J. In 1985 nearly 1,700 persons who had exposure to diethylstilbestrol (DES)--520 mothers, 1,079 daughters, and 94 sons--responded to a mailed questionnaire about their general health status. Results were compared with responses to the 1985 National Health Interview Survey and other population-based studies. As with research findings in animals, conditions that suggest possibly impaired immune **function--that is, respiratory tract infections, asthma, arthritis, and lupus--were reported more frequently among the persons with DES exposure. Conditions that may involve altered endocrine function were also more frequent** among such

persons. Given the biased sample, findings from this preliminary survey are seen as guidelines to areas meriting more rigorous research.

Stress 1999 Dec;3(2):163-71. **Acute stress persistently enhances estrogen levels in the female rat.** Shors TJ, Pickett J, Wood G, Paczynski M.

Lancet 1988 Sep 17;2(8612):684. **Progesterone for premenstrual exacerbations of asthma.** Dalton K.

Lancet 1988 Aug 13;2(8607):370-2. **Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone.** Beynon HL, Garbett ND, Barnes PJ. Three patients with severe premenstrual exacerbations of asthma are reported. None had responded to conventional treatment, including high-dose corticosteroids. In all cases there was a striking fall premenstrually in peak flow rate. **The addition of intramuscular progesterone (100 mg daily in two cases and 600 mg twice a week in one) to the regimen eliminated the premenstrual dips in peak flow,** and daily doses of prednisolone were reduced in the three patients.

C R Seances Soc Biol Fil 1981; 175(2):247-52. **[Influence of estrogens on histamines liberation by whole blood induced by allergens in vitro].** [Article in French] Terral C, Godard P, Michel FB, Macabies J. "A relapse of bronchial obstruction during women's menstrual cycle in often observed. Incubating blood and **rising rates of estrogens produce an increase of histamine-release** induced by allergens."

Am J Respir Crit Care Med 1995 Oct;152(4 Pt 1):1183-8. **Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study.** Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. We prospectively evaluated the association of hormone replacement therapy and asthma incidence in a cohort of pre- and postmenopausal women 34 to 68 yr of age. **During 582,135 person-years of follow-up between 1980 and 1990, 726 new cases of asthma were documented. Postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women (relative risk = 0.65;** 95% confidence interval [CI] = 0.46 to 0.92). Among naturally menopausal women, the age-adjusted relative risk of asthma for ever use of postmenopausal hormones was 1.49 (95% CI = 1.10 to 2.00); for current use of hormones (conjugated estrogens with or without progesterone), 1.50 (95% CI = 0.98 to 2.30); and for past use, 1.52 (95% CI = 1.08 to 2.13), compared with never use of hormones. **Ever users of 10 or more years' duration had twice the age-adjusted risk of asthma compared with women who never used postmenopausal hormones** (95% CI = 1.39 to 2.87). Among current users of **conjugated estrogens, there was a positive dose-response demonstrated between daily dose and asthma risk (p for trend = 0.007). While confirmatory studies are warranted, these data suggest that estrogen plays a role in the pathophysiology of asthma and that long-term use and/or high doses of postmenopausal hormone therapy increase subsequent risk of asthma.**

J Microbiol Immunol Infect 1998 Sep;31(3):197-9. **Premenstrual asthma: report of a case with hormonal studies.** Lam SM, Huang SC. "Daily peak flow readings and every other day hormonal studies of progesterone and estrogen both **demonstrated a positive correlation between the serum progesterone and the peak flow readings.** The addition of intramuscular progesterone (75 mg daily) to the bronchodilators eliminated the premenstrual dips in peak flow, and daily doses **of prednisolone were reduced to 5-10 mg. We suggest that a rapid fall in serum progesterone may play an important role in the pathogenesis of premenstrual asthma."**

Int Rev Immunol 1998;16(5-6):635-49. **The chronobiology of human cytokine production.** Petrovsky N, Harrison LC. "Cytokine production in human whole blood exhibits diurnal rhythmicity. Peak **production of the pro-inflammatory cytokines IFN-gamma, TNF-alpha, IL-1 and IL-12 occurs during the night and early morning at a time when plasma cortisol is lowest. The existence of a causal relationship between plasma cortisol and** production is suggested by the finding that elevation of plasma cortisol within the physiological range by the administration of cortisone acetate results in a corresponding fall in pro-inflammatory cytokine production. Cortisol may not be the only neuroendocrine hormone that entrains cytokine rhythms; other candidates include 17-hydroxy progesterone, melatonin and dihydroepiandrostene dione (DHEAS). The finding of diurnal cytokine rhythms may be relevant to **understanding why immuno-inflammatory disorders such as rheumatoid arthritis or asthma exhibit night-time or early morning exacerbations and to the optimisation of treatment for these disorders."** "Finally, diurnal rhythmicity of immune function suggests that the nature of an immune response, for example in response to vaccination, may be modified by the time of day of antigen administration and raises the possibility that immune responses could be therapeutically manipulated by co-administration of immuno-regulatory hormones such as glucocorticoids."

J Asthma 1999 Sep;36(6):511-7. **Asthma and geographical altitude: an inverse relationship in Mexico.** Vargas MH, Sienra-Monge JJ, Diaz-Mejia G, DeLeon-Gonzalez M. mhvargas@mailer.main.conacyt.mx Motivated by the great asthma-prevalence variation throughout the world, we analyzed the rate variation of medical services due to asthma in the 32 Mexican states at the Instituto Mexicano del Seguro Social (approximately 24 million **insured subjects). In 1993, a total of 406,036 services were due to asthma, and state rates ranged from 53 to 476 x 10,000 insured subjects. A direct** correlation ($p < 0.05$) was found for single-room house, ascariasis, and rubella rates, but the strongest (inverse) correlation was found for geographical altitude ($r = -0.73$, $p < 10(-5)$). Thus, in Mexico, geographical altitude affects the etiological factor(s) responsible for the development of asthma or for the triggering of asthma attacks.

Allergy Asthma Proc 1998 Sep-Oct; 19(5):263-9. **Effect of sex hormones on eosinophilic inflammation in nasal mucosa.** Hamano N, Terada N, Maesako K, Numata T, Konno A. We examined the effects of sex hormones on the functions of eosinophils. Treatment of eosinophils with beta-estradiol significantly enhanced the eosinophil adhesion to human mucosal microvascular endothelial cells (HMMEC), and eosinophils stimulated by a combination of beta-estradiol and progesterone showed significant induced degranulation. On the other hand, testosterone significantly reduced the eosinophil adhesion to HMMEC and eosinophil viability. The experiments from the series of studies might provide a partial explanation for the aggravation of asthma and some forms of rhinitis that occurs during pregnancy.

Allergy Asthma Proc 1998 Sep-Oct; 19(5):263-9. **Effect of sex hormones on eosinophilic inflammation in nasal mucosa.** Hamano N, Terada N, Maesako K, Numata T, Konno A. We examined the effects of sex hormones on the functions of eosinophils. **Treatment of eosinophils with beta-estradiol significantly enhanced the eosinophil adhesion to human mucosal microvascular endothelial cells (HMMEC), and eosinophils stimulated by a combination of beta-estradiol and progesterone showed significant induced degranulation. On the other hand, testosterone** significantly reduced the eosinophil adhesion to HMMEC and eosinophil viability. The experiments from the series of

studies might provide a partial explanation for the aggravation of asthma and some forms of rhinitis that occurs during pregnancy.

Ann Allergy Asthma Immunol 1998 Sep;81(3):243-6. **Exacerbation of premenstrual asthma caused by an oral contraceptive.** Derimanov GS, Oppenheimer J. "No other precipitating factors were identified. After discontinuing the contraceptives, her condition returned to baseline."

Pediatr Allergy Immunol 1997 Nov;8(4):200-4. **Is asthma an endocrine disease?** Wjst M, Dold S. The prevalence of pediatric asthma has increased in many parts of the world. This increase started more than 30 years ago and is particularly obvious in studies which document the onset of asthma in native populations when they change to a "Western" lifestyle. Besides a genetic influence, numerous environmental factors have been described for the development of asthma. **Genetic factors are unlikely to explain the sharp increase within the short time period and also allergen and pollution exposure or any specific infection does not actually seem to be the main cause for this phenomenon. Another factor, however, that fits well into the geographical and temporal background of the asthma epidemic is the mother's oral contraceptive use.** We therefore review the epidemiological association with later asthma in the children, give a summary of estrogen effects on immune function and develop a preliminary theory how oral contraception could influence later pregnancy.

Ann Allergy Asthma Immunol 1999 Sep;83(3):222-8. **Perimenstrual alterations in type-1/type-2 cytokine balance of normal women.** Agarwal SK, Marshall GD Jr. "Several immune-based diseases, such as **asthma, have significant clinical exacerbations during specific intervals of the menstrual cycle and are associated with oral contraceptive pills (OCRs)."** "The perimenstrual decrease in the IFN-gamma: IL-10 ratio was observed in women not taking OCP, but not in women taking OCP. Furthermore, the OCP group had a lower mid-cycle IFN-gamma: IL-10 ratio compared with the control group."

Compr Ther 2001 Spring;27(1):65-71. **Menstrual cycle effects on common medical conditions.** Case AM, Reid RL. "Menstrual cycle-related exacerbation of common medical conditions such as **migraine, epilepsy, asthma, irritable bowel syndrome, and diabetes, is a well-recognized phenomenon."**

J Affect Disord 2001 Mar;63(1-3):85-92. **The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system.** Maes M, Ombelet W, De Jongh R, Kenis G, Bosmans E. "There is now evidence that some patients with major depression show an activation of the inflammatory response system (IRS)." "Serum IL-6, sIL-6R, sIL-1RA were significantly higher 1 and 3 days after delivery than before. Women who had suffered from a lifetime history of major depression had greater increases in serum IL-6 and sIL-1RA in the early puerperium than women without a lifetime history. Women who had suffered from a lifetime history of major depression had significantly higher IL-6, and sIL-1RA concentrations 1 and 3 days after delivery than women with a negative life-time history." "The responses of IL-6 and sIL-1RA following delivery are amplified in women who previously suffered from major depression."

J Appl Physiol 2001 Aug;91(2):703-8. **Inhibition of nitric oxide synthesis attenuates thermally induced asthma.** Kotaru C, Skowronski M, Coreno A, McFadden ER Jr. **"The results of this study demonstrate that NO generated from the airways of asthmatic individuals may play an important role in the pathogenesis of thermally induced asthma."**

C R Seances Soc Biol Fil 1995;189(3):389-400. **[Does nitric oxide stress exist?]** [Article in French] Torreilles J, Guerin MC. "Ten years ago, the term "oxidative stress" (sigma -O2) was created to define oxidative damage inflicted to the organism. This definition brings together processes involving reactive oxygen species production and action such as free radical production during univalent reduction of oxygen within mitochondria, activation of **NADPH-dependent oxidase system on the membrane surface of neutrophils, flavoprotein-catalyzed redox** cycling of xenobiotics and exposure to chemical and physical agents in the environment. Since the discovery of the nitric oxide biosynthetic pathway, the deleterious effects of uncontrolled nitric oxide generation are generally classified as oxidative stress." ". . . modification of SH-groups of glyceraldehyde-3-phosphate dehydrogenase in a cGMP-independent mechanism: by this way, NO in excess can strongly inhibits this important glycolytic enzyme and reduce the cellular energy production." ". . . LPS-induced overproduction of NO has been shown to inhibit cytochrome P450-dependent metabolism and to mediate the suppression of hepatic metabolism." "Overstimulation of NO synthases might therefore contribute to pathophysiological **states such as: gastrointestinal motility, reflux oesophagitis, asthma, adult respiratory distress syndrome (ARDS) and chronic pulmonary artery hypertension. To these NO-mediated biological functions, one could add the biological effects of NO-derivatives such as N-nitrosocompounds, which act as carcinogenic agents. . . ."**

Biull Eksp Biol Med 1976 Oct;82(10):1181-3. **[Role of the biological activity of serotonin in the production of the "shock lung" syndrome.]** [Article in Russian] Bazarevich GI, Deviataev AM, Likhtenshtein AO, Natsvlishvili BP, Sadeko MK. The influence of the serotin biological activity on forming the "shock" lung syndrome was revealed in experiments on rats. Tachyhyperpnea with predominance **of functional emphysema** and a small number of atelectic tissue areas were observed in the animals with traumatic "shock" during the serotonin hypersecretion. Tachyhypopnea with a significant predominance of atelectiv areas was seen during the serotonin hypoproduction.

J Clin Pharmacol 1995 Jun;35(6):541-72. **Serotonin and serotonin antagonism in cardiovascular and non-cardiovascular disease.** Frishman WH, Huberfeld S, Okin S, Wang YH, Kumar A, Shareef B.

Epidemiology 2001 Mar;12(2):200-8. **Air pollution and exacerbation of asthma in African-American children in Los Angeles.** Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. **"Significant increases in asthma morbidity and mortality in the United States have occurred since the 1970s, particularly among African-Americans."**

Toxicology 2000 Nov 2;152(1-3):31-5. **Endotoxins, asthma, and allergic immune responses.** Lapa e Silva JR, Possebon da Silva MD, Lefort J, Vargaftig BB.

J Allergy Clin Immunol 2000 Dec; 106(6):1081-7. **Role of endogenous nitric oxide in exercise-induced airway narrowing in patients with bronchial asthma.** Kanazawa H, Hirata K, Yoshikawa J. "Increased amounts of nitric oxide (NO) in expired air and induced sputum have been found in asthmatic patients . . . ." "These findings suggest that excessive production of NO is associated with EIB in patients with asthma and contributes to the prolonged airway narrowing phase rather than to the maximal airway narrowing evoked by exercise."

Eur Respir J 1997 Feb;10(2):482-91. **The role of pulmonary surfactant in obstructive airways disease.** Hohlfeld J, Fabel H, Hamm H. "Pulmonary surfactant research has an increasing impact on treatment **considerations in adult respiratory disorders,**

above all acute respiratory distress syndrome (ARDS)." "In addition to its surface activity, airway surfactant improves bronchial clearance and regulates airway liquid balance, thus indirectly modulating airway wall thickness and airway diameter. Surfactant has furthermore been shown to modulate the function of respiratory inflammatory cells. Its immunomodulatory activity includes suppression of cytokine secretion and transcription factor activation. This may be of importance in the inflammatory network of asthma."

Respir Physiol 1998 Apr;112(1):113-9. **Worsening of hypoxemia with nitric oxide inhalation during bronchospasm in humans.** Takahashi Y, Kobayashi H, Tanaka N, Honda K, Kawakami T, Tomita T. **"Our results show that NO inhalation worsens desaturation during bronchospasm in humans after MCh nebulization."**

Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1997 Sep;118(1):5-10. **Inhibitory effect of sex steroids on guinea-pig airway smooth muscle contractions.** Perusquia M, Hernandez R, Montano LM, Villalon CM, Campos MG. perusqui@servidor.unam.mx We assessed the possible inhibition of airway smooth muscle contraction by progesterone and pregnanolones (5 alpha and 5 beta-reduced). Progesterone and 5 **beta-pregnanolone prevented histamine- or carbachol-induced contraction in isolated guinea-pig trachea and potency was related to their respective chemical structure; progesterone was the most potent inhibitor in a concentration-dependent manner.** The steroids also exhibited calcium antagonist activities in this tissue as assessed by their action on calcium entry in depolarized preparations; this event involved the immediate blockade of the extracellular calcium influx in the muscle cell membrane, indicating a nongenomic action. Classical GABAA antagonists did not block the progesterone response, implying no involvement of the GABAA-receptor complex. Our results **suggest a bronchodilating effect induced by sex steroids, and probably by other related compounds, before the genomic mechanisms take place. This nongenomic** action of steroids could have potential therapeutic usefulness in the treatment of asthma.

Am J Respir Crit Care Med 1997 Apr;155(4):1273-7. **Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill.** Tan KS, McFarlane LC, Lipworth BJ.

Verh K Acad Geneeskd Belg 1991;53(5):497-505. **[Consumption of coca in history.]** [Article in French] Appelboom T. "The **medical use of cocaine for the treatment of hayfever and asthma (Dr. Tucker's elixir) had in between officially been agreed by the famous scientific societies in America."**

Cardiology 2001;95(1):31-4. **Insulin resistance is increased by transdermal estrogen therapy in postmenopausal women with cardiac syndrome X.** Assali AR, Jabara Z, Shafer Z, Solodky A, Herz I, Sclarovsky E, Strasberg B, Sclarovsky S, Fainaru M. ". . . it remains to be examined how short-term transdermal estrogen therapy (TET) affects insulin **sensitivity** (SI) in patients with cardiac syndrome X (CSX), who are characterized by elevated insulin resistance." **"SI decreased by 32 +/- 8.3%, from 5.94 +/- 1.14 at baseline to 3.61 +/- 0.40 [(10(-4) x min(-1))/(microU/ml)] during TET** ($p = 0.03$)."

Am J Physiol Lung Cell Mol Physiol 2001 Sep;281(3):L668-76. **Airway inflammation in nonasthmatic amateur runners.** Bonsignore MR, Morici G, Riccobono L, Insalaco G, Bonanno A, Profita M, Paterno A, Vassalle C, Mirabella A, Vignola AM. marisa@ifr.pa.cnr.it **"Elite athletes show a high prevalence of symptoms and signs of asthma, but no** study has assessed the acute effects of endurance exercise on airway cells in nonasthmatic athletes." "After the marathon, exhaled NO (n = 9 subjects) was higher [27 +/- 9 parts/billion (ppb)] than at baseline (12 +/- 4 ppb; $P < 0.0005$). Polymorphonuclear neutrophil (PMN) counts in induced sputum were much higher in runners (91.2 +/- 3.6% of total cells postmarathon and 78.7 +/- 9.1% at baseline) than in sedentary control subjects (9.9 +/- 5.9%; $P < 0.001$)." "Our data indicate that sputum PMNs are increased in nonasthmatic runners both after a marathon and at baseline and suggest that NO may modulate exercise-associated inflammatory airway changes."

J Allergy Clin Immunol 2000 Sep;106(3):444-52. **Allergy and asthma in elite summer sport athletes.** Helenius I, Haahtela T. **"In the summer Olympic Games, 4% to 15% of the athletes showed evidence of asthma or used antiasthmatic medication. Asthma is most commonly found in endurance** events, such as cycling, swimming, or long-distance running. The risk of asthma is especially increased among competitive swimmers, of which 36% to 79% show bronchial hyperresponsiveness to methacholine or histamine. The risk of asthma is closely associated with atopy and its severity among athletes. A few studies have investigated occurrence of exercise-induced bronchospasm among highly trained athletes. The occurrences of exercise-induced bronchospasm vary from 3% to 35% and depend on testing environment, type of exercise used, and athlete population tested. Mild eosinophilic airway inflammation has been shown to affect elite swimmers and cross-country skiers. This eosinophilic inflammation correlates with clinical parameters (ie, exercise-induced bronchial symptoms and bronchial hyperresponsiveness). Athletes commonly use antiasthmatic medication to treat their exercise-induced bronchial symptoms."

Am J Respir Crit Care Med 2001 Sep 1;164(5):785-9. **Repeated hyperventilation causes peripheral airways inflammation, hyperreactivity, and impaired bronchodilation in dogs.** Davis MS, Freed AN. "Winter athletes have an increased incidence of asthma, suggesting that repetitive hyperventilation with cold air may predispose individuals to airways disease. We used a canine model of exercise-induced hyperpnea to examine the effects of repeated hyperventilation with cool, dry air (i.e., dry air challenge [DAC]) on peripheral airway resistance (Rp), reactivity, and inflammation." ". . . other mechanisms in addition to increased smooth muscle tone may contribute to the development of repetitive hyperventilation-induced bronchial obstruction and hyperreactivity."

Exerc Immunol Rev 2001;7:66-89. **Free radicals, exercise, apoptosis, and heat shock proteins.** Fehrenbach E, Northoff H. "Evidence is accumulating that free radicals have important functions in the signal network of cells. . . ." **"Excessive exercise will also induce DNA damage in peripheral leukocytes."** "Massive intervention into the redox state by pharmaceutical doses of exogenous antioxidants should be regarded with caution due to the ambiguous role of free radicals in regulation of growth, apoptosis, and cytotoxicity by immunocompetent cells."

Med Sci Sports Exerc 2000 Aug; 32(8):1384-9. **Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing.** Henson DA, Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Shannon M, Bolton MR, Davis JM, Gaffney CT, Kelln WJ, Austin MD, Hjertman JM, Schilling BK. "This study examined the influence of carbohydrate (C) versus placebo (P) beverage ingestion on the phagocytic and cytokine responses to normal rowing training by 15 elite female rowers." "Concentrations of blood neutrophils and monocytes, phagocytic activity, and plasma IL-1ra were significantly lower postexercise after C versus P ingestion." **"These data indicate that carbohydrate compared with placebo ingestion attenuated the moderate rise in blood neutrophils, monocytes, phagocytosis, and plasma IL-1ra**

concentrations that followed 2-h bouts of training in elite female rowers."

J Clin Hypertens (Greenwich) 2001 May-Jun;3(3):145-52. **Gender differences in vascular compliance in young, healthy subjects assessed by pulse contour analysis.** Winer N, Sowers JR, Weber MA. "Reductions in the oscillatory or reflected component of the diastolic waveform have been observed in various clinical conditions, including hypertension, diabetes mellitus, and congestive heart failure, and may reflect endothelial dysfunction at the site of resistance vessels." **"These data indicate that female sex hormones have unexpected negative effects on small vessel compliance. They may help to explain why premenopausal women hospitalized for myocardial infarction have higher mortality rates than men of the same age."**

J Leukoc Biol 1993 Apr;53(4):420-6. **Polyunsaturated fatty acids increase neutrophil adherence and integrin receptor expression.** Bates EJ, Ferrante A, Harvey DP, Poulos A. Department of Immunology, Women's and Children's Hospital, Adelaide, Australia. Fish oils are abundant in polyunsaturated fatty acids of the n-3 series (in particular eicosapentaenoic, 20:5 and docosahexaenoic acid, 22:6). Such fatty acids are generally considered to be beneficial in the prevention of cardiac disease and to have anti-inflammatory properties. **Neutrophil adherence is an essential early event in an acute inflammatory response, and we have demonstrated that both 20:5 and 22:6 stimulate adherence in vitro. Arachidonic acid (20:4, n-6) was also stimulatory. Significant simulation of adherence was seen from 5 to 80 microM (nontoxic concentrations) 22:6, 20:5, or 20:4. At the lower fatty acid concentrations tested (< or = 40 microM) 20:5 was less active than 22:6 or 20:4 at stimulating adherence. Above 40 microM there was no difference in the ability of the three fatty acids to stimulate adherence**. At the lower fatty acid concentrations tested (< or = 10 microM) 22:6 was less active than 20:4, whereas above 10 microM they were equally active. Immunofluorescent flow cytometric analysis of neutrophil integrin (adherence) receptors showed that **the complement C3bi receptor (CD11b) was up-regulated by these fatty acids.** There was no change in CD11a or CD11c. Saturated fatty acids of the same chain length were without effect on adherence or receptor expression. The findings suggest that **these polyunsaturated fatty acids may, under certain conditions, be proinflammatory with respect to their acute effects on the interaction of neutrophils with microbes, endothelium, and other tissues.**

Nippon Yakurigaku Zasshi 2001 Sep;118(3):170-6. **[New strategy on medical research after completion of genome sequencing].** [Article in Japanese] Ishikawa K, Tsujimoto G.

J Investig Allergol Clin Immunol. 2001;11(2):73-8. **Susceptibility genes for asthma and allergy: hits and questions.** Castro J, Telleria JJ, Blanco-Quiros A.

J Asthma. 1989;26(6):331-3, 335-40. **The new gestalt: asthma as a chronic inflammatory disease.** Ackerman SJ.

Med Sci Sports Exerc 2001 Apr;33(4):549-55. **Anaerobic exercise induces moderate acute phase response.** Meyer T, Gabriel HH, Ratz M, Muller HJ, Kindermann W.

Epilepsia 2000 May;41(5):510-5. **Estradiol facilitates kainic acid-induced, but not flurothyl-induced, behavioral seizure activity in adult female rats.** Woolley CS.

Endocrinology 1992 Aug;131(2):662-8. **Estradiol selectively regulates agonist binding sites on the N-methyl-D-aspartate receptor complex in the CA1 region of the hippocampus.** Weiland NG. **"Estradiol alters cognitive function and lowers the threshold for seizures in women and laboratory animals. Both of these activities are modulated by the excitatory neurotransmitter glutamate in the hippocampus."** "Two days of estradiol treatment increased the density of NMDA agonist, but not of competitive nor noncompetitive NMDA antagonist binding sites exclusively in the CA1 region of the hippocampus. The density of noncompetitive NMDA antagonist sites, however, was decreased in the dentate gyrus by estradiol treatment." "The increase in NMDA agonist sites with ovarian hormone treatment should result in an increase in the sensitivity of the hippocampus to glutamate activation which may mediate some of the effects of estradiol on learning and epileptic seizure activity."

Epilepsia 1985 May-Jun;26(3):252-7. **Comparative effects of estradiol benzoate, the antiestrogen clomiphene citrate, and the progestin medroxyprogesterone acetate on kainic acid-induced seizures in male and female rats.** Nicoletti F, Speciale C, Sortino MA, Summa G, Caruso G, Patti F, Canonico PL. We have investigated the comparative effects of estradiol benzoate (EB), the antiestrogen clomiphene citrate (CC), and the progestin medroxyprogesterone acetate (MPA) on seizures induced by systemic injection of kainic acid (15 mg/kg i.p.) in male and female rats. **Subcutaneous administration for 10 days of EB (10 micrograms/kg) or high doses of CC (50 mg/kg) significantly potentiated kainate-induced seizures,** with this effect being more pronounced in male animals. Doses of 2.5 mg/kg of CC potentiated kainate-induced seizures in male rats but were ineffective in female rats. **Low doses of CC (0.5 mg/kg) exhibited a mild anticonvulsant effect in both sexes. Repeated administration of MPA (2.5 mg/kg) partially protected female animals against kainate-induced seizures;** in male animals, MPA induced a 30% increase in the seizure severity score, although the difference from the score of control male rats **was not significant.** These data suggest that sex steroids influence kainate-induced seizures in a sex-dependent manner and that the effects of the antiestrogen CC are dose dependent. This should be taken into account in view of a possible use of CC and MPA in hormonal therapy for seizure disorders.

Biochem Soc Symp 1999; 66:149-66. **Mitochondrial dysfunction in sepsis.** Singer M, Brealey D. **"The current mainstream view of organ failure induced by sepsis revolves around inflammation and loss of vascular control. However, there has been a resurgence in interest in bioenergetic failure due to mitochondrial**

dysfunction. This concept is not new--studies date back 30 years. . ." "As a generalization, there does appear to be depression of mitochondrial function with longer-duration models of greater severity." "The potential roles of nitric oxide, intracellular calcium and reactive oxygen species are highlighted."

J Clin Invest 1985 Jul;76(1):66-74. **Hamster female protein, a sex-limited pentraxin, is a constituent of Syrian hamster amyloid.** Coe JE, Ross MJ. Female protein (FP) is a pentraxin of Syrian hamster which is a homologue of two human pentraxins, C-reaction protein (CRP) and amyloid P component (AP).

Am J Pathol 2001 Mar;158(3):1039-51. **Generation of C-reactive protein and complement components in atherosclerotic plaques.** Yasojima K, Schwab C, McGeer EG, McGeer PL. "C-reactive protein (CRP) and complement are hypothesized to be major mediators of inflammation in atherosclerotic plaques."

Jpn J Pharmacol 1979 Aug;29(4):509-14. **Anti-inflammatory action of progesterone on carrageenin-induced inflammation in rats.** Nakagawa H, Min KR, Nanjo K, Tsurufuji S. Effect of progesterone (1 mg/kg) on the inflammation in rats induced by carrageenin was studied. **Progesterone inhibited the vascular permeability and the formation of granulation tissue in the early phase of the inflammation. In the chronic proliferative phase, progesterone suppressed the vascular permeability and there was an active resorption of the granulation tissue.** Increased degradation of noncollagen protein was observed in the treated group without apparent influence on the metabolism of collagen or on the synthesis of noncollagen protein. **The mode of action of progesterone was compared with that of a potent anti-inflammatory steroid, hydrocortisone acetate.**

Circulation 1999 Aug 17;100(7):717-22. **Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study.** Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, Sakkinen PA, Tracy RP. "**Postmenopausal hormones rapidly increased the concentration of the inflammation factor C-reactive protein. Such an effect may be related to adverse early effects of estrogen therapy.**"

J Clin Endocrinol Metab 2001 Sep; 86(9):4216-22. **Differential effects of E and droloxifene** on C-reactive protein and other markers of inflammation in healthy postmenopausal women. Herrington DM, Brosnihan KB, Pusser BE, Seely EW, Ridker PM, Rifai N, MacLean DB. "**E treatment resulted in 65.8% higher levels of C-reactive protein (P = 0.0002) and 48.1% higher levels of IL-6 (P < 0.001),** . . ."

Arterioscler Thromb Vasc Biol 2001 Feb;21(2):255-61. **Tamoxifen and cardiac risk factors in healthy women: Suggestion of an anti-inflammatory effect.** Cushman M, Costantino JP, Tracy RP, Song K, Buckley L, Roberts JD, Krag DN.

Circulation 1999 Aug 17;100(7):713-6. **Hormone replacement therapy and increased plasma concentration of C-reactive protein.** Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE.

JAMA 2001 Jul 18;286(3):327-34. **C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.** Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM.

Thromb Haemost 1999 Jun;81(6):925-8. **Increased C-reactive protein levels during short-term hormone replacement** therapy in healthy postmenopausal women.

Immunol Lett 1991 Jan;27(1):75-9. **Parallel relationship between the increase in serotonin in the liver and the hypoglycaemia induced in mice by interleukin-1 and tumour necrosis factor.** Endo Y.

Clin Sci (Colch) 2000 Jan;98(1):47-55. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Jeukendrup AE, Vet-Joop K, Sturk A, Stegen JH, Senden J, Saris WH, Wagenmakers AJ.

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Ray Peat's Newsletter

What is now proved was once only imagin'd.

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Homeostasis and Aging

Thyroid mysteries and minerals: Cramps, excitotoxicity, dementia, and CO2

Blood perfusion of the brain and heart and muscles is increased by carbon dioxide, which is logical, considering that carbon dioxide ordinarily rises during metabolic activation. But the kidneys don't have this simple response to carbon dioxide, and this seems to be because of the special role of carbon dioxide in homeostasis and kidney function.

Blood flow to the kidneys is regulated by nerves and hormones. Parathyroid hormone and growth hormone cause vasodilation in the kidney, and increase its blood flow. The increased flow tends to produce a more dilute, hypotonic urine. In the kidneys, carbon dioxide's effects are much more complex than just regulating blood flow, and the kidneys maintain a remarkably high concentration of CO_2, causing some people to argue that they concentrate it from the blood.

About 88 years ago, W. F. Koch (who is known for his cancer therapy) studied the parathyroid hormone and its relation to tetany (prolonged muscle contraction) and convulsions, and was able to demonstrate that the major minerals, sodium, potassium, magnesium, and calcium are to some extent interchangeable in alleviating the tetany and convulsions produced by removal of the parathyroid gland, though magnesium was the most effective. This work was ignored by those who wanted to establish a simple relationship between "one gland, one hormone, one mechanism, one symptom or disease." A. J. Carlson's group promoted the idea that the parathyroid hormone's function was simply to increase the amount of calcium in the blood, and that it was calcium which prevented tetany. This doctrine has had far-reaching consequences.

The view which has come to dominate twentieth century biology is that organisms were assembled by a simple-minded watchmaker named Natural Selection, and that they can be understood by reducing them to their simple parts, the way we understand a watch or a motor. A polar opposite to that view would be that nature is infinite, but knowable. To understand Koch's step from tetany to cancer isn't possible within the conventions of ordinary "medical endocrinology," but Koch assumed that nature hadn't learned its methods in medical school. Koch postulated, early in the century, that electrons and free radicals were involved in the most important biological processes—respiration, movement, immunity, regeneration, etc. He was probably the first person to apply the subtleties of organic chemistry (such as the activation of chemical groups by nearby groups) to biology. (Electronic induction.) Albert Szent-Gyorgyi, a Hungarian aristocrat, recognized the complexity of nature and tried to work out a detailed scientific explanation for the ideas postulated by Koch. Szent-Gyorgyi, following Koch's interest in free radical color changes and fluorescence, understood that certain biological pigments represented special *interactions of electrons and photons with proteins,* and that muscle contraction wasn't just "a mechanical process," but probably involved all of the processes that distinguish life from death.

Books by William Frederick Koch:
Cancer and its Allied Diseases, 1926.
Natural Immunity, 1934.
The Chemistry of Natural Immunity, 1939.
The Survival Factor in Cancer and Viral Infections, 1955, 1958.

For both Koch and Szent-Gyorgyi, contraction, respiration, and cancer were life processes that required understanding the interactions of water, electrons, and proteins. Practically all other biologists ridiculed their interest in water and electrons.

(One of Szent-Gyorgyi's major projects in studying the role of respiratory energy in muscle contraction involved a strain of goat that suffers from myotonia, or chronic and generalized excessive muscle tension. I suspect that Koch's work with tetany led him in this direction.)

Szent-Gyorgyi found that progesterone and estrogen have antagonistic effects on the heart, and explained progesterone's similarity to digitalis by suggesting that it helps the cells to "build structure." The structure that he referred to in the muscle cell was the structure made up of "structured water" and proteins and regulatory substances. Carbon dioxide's concentration affects the structural energy content of the protein-water system, and this effect can nicely account for many of the mysteries of cellular heat production, including the negative heat observed in certain stages of nerve and muscle activity. Szent-Gyorgyi used a variety of electron/photon/chemical interactions to demonstrate that intracellular water has special structural properties. This line of thinking led him to a view of ionic regulation (1957) similar to Gilbert Ling's, and probably contributed to Linus Pauling's similar ideas (1960). (Szent-Gyorgyi never publicly acknowledged his respect for Koch's work, since he was obviously aware of the great dangers from the coalition of the medical-pharmaceutical establishment, the FBI, and organized crime, which drove Koch out of the United States. During the decade in which Koch operated his clinic in Detroit, it was the only large city in the U.S. in which cancer mortality declined; while cancer mortality in Los Angeles was rising by 30%, in Detroit it was declining by 20%. Immediately after the Koch episode, the same alliance conspired against Andrew Ivy and the Durovic brothers to steal the anticancer drug they called Krebiozen, but in Koch's case, they couldn't figure out just what to steal, so they tried to kill him or put him in jail. A. J. Carlson, incidentally, had a prominent role in the conspiracy against Ivy.)

Instead of receptors and effectors, locks and keys, motors and pumps, all built up arbitrarily by natural selection, the coherent view of the organism is that the **fundamental properties of matter are used and amplified and focussed by processes of tuning and balancing.** It is the "subtle reactivity" of the living system which maintains the adaptive organization of energy and structure. Part of the reactivity of the organism is the flexibly interactive metabolism, which adaptively distributes substance and energy. Ordinary metabolism, by *adjusting the affinities of the cell substance,* can account more rationally for the processes that are called "homeostatic" than the hypothetical apparatus of "pumps" and "channels," which are biology's *deus ex machina,* proposed whenever needed.

The doctrine of "one gland-one action" caused people to focus on the low blood calcium which occurs in the tetany which is brought on by removal of the parathyroid gland (which sometimes killed patients when their thyroids were removed, along with the associated parathyroids). By the 1920s, surgeons were careful about avoiding damage to the parathyroids to avoid tetany, but tetany kept occurring. They began leaving part of the thyroid gland, too, but tetany still occurred in a significant portion of patients. In fact, tetany is a risk following other operations, such as removal of the gall bladder. A new explanation for post-thyroidectomy tetany was invented, "the hungry bone syndrome," based on the idea that hyperthyroidism robs the bones of calcium, and that the bones begin stealing calcium from the rest of the body when the gland is removed. However, animal experiments show that it is only synthetic thyroxin which causes bone to lose calcium, and that the natural thyroid hormone, T_3, stimulates bone growth; also, euthyroid patients can experience tetany following removal of their thyroid.

Practically any kind of poisoning causes cells to take up calcium from the blood, so the finding of hypocalcemia in association with tetany might permit people to confuse effect with cause!

Tetanic associated ↓ Calcium

(1) Guanidine + methylguanidine + Ammoniaque = Convulsion en agissant sur les recepteurs des ac. aminé excitatrice

The doctrine of hypocalcemic tetany led to the practice of treating tetany with intravenous calcium solutions; for example, veterinarians often treat cows' "grass tetany" with large intravenous doses of calcium. The treatment works, but the tetany is now attributed to a magnesium deficiency (since magnesium supplementation works better, as Koch discovered), and excessive ammonia produced in the cow's rumen can contribute to the magnesium deficiency. The facts that have grown up in veterinary research have a strong parallel to Koch's ideas presented around 1912.

Koch found that the **convulsions produced by removal of the parathyroid glands were associated with the development of nephritis and the appearance of the toxic substances, guanidine and methylguanidine.** These compounds, and ammonia, are now known to produce convulsions by acting on the "excitatory amino acid receptors." These excitatory receptors release calcium into the cytoplasm, activating many cell processes, including the liberation of fatty acids and the breakdown of proteins. When these "receptors" are activated, the cells' energy requirement increases, and glucose is consumed more rapidly. Whenever these "receptors" are activated, magnesium will protect the cell from the "toxic" excitation. Effective antidotes to the excitotoxins have been based on their blocking of these "receptors." Amantadine is now known for its neuroprotective activity, as well as its anticholinergic and antiviral effects. In the 1950s, toxins based on the guanidine group (e.g., phenformin) were introduced to treat diabetes, because they can lower blood sugar, but they were later withdrawn because they killed the patients too quickly.

Carbon dioxide, produced by respiratory use of glucose, suppresses glycolysis, and so spares sugar. Carbon dioxide is also combined with ammonia, detoxifying it into urea. Although it hasn't been determined, I suspect that Koch's "toxic amines" are detoxified by their direct combination with carbon dioxide, which spontaneously reacts with amines to form carbamino groups. When there isn't enough carbon dioxide to combine with ammonia, the ammonia can combine with ketoglutarate, from the Krebs cycle, interfering with respiration at the same time that it produces the excitatory glutamic acid. Ammonia, in chronic poisoning, rather than producing convulsions, produces stupor and coma, and at this point, its combination with glutamic acid to produce glutamine is probably important as a defense against seizures, eliminating both ammonia and glutamic acid.

Hyperventilation, in which too much carbon dioxide is "blown off," causes tetany, and in susceptible people, can cause convulsions. Hyperventilation causes constriction of the bronchial muscles and thickening of mucus, producing symptoms of asthma. It causes contraction of blood vessels in the heart, weakening the pumping action, while blood vessels in the general circulation also constrict, raising blood pressure and reducing circulation. Hyperventilation commonly causes arrhythmia, and thickens the blood. The loss of carbon dioxide reduces brain circulation, creating complex paresthesias and stroke symptoms. "Hyperventilation" is a relative term, and refers to the amount of carbon dioxide which is lost from the blood. Heavy, rapid breathing at high altitude or in the presence of a carbon dioxide-rich atmosphere, doesn't necessarily constitute hyperventilation.

Water, proteins, oxygen, and minerals, are all crucially regulated by carbon dioxide. The enzyme, carbonic anhydrase, which is regulated by hormones (including the parathyroid hormone) and nerves, accelerates the interchange between carbon dioxide and bicarbonate, each of which has special functions. Bicarbonate is more soluble in water, but carbon dioxide is more soluble in living substance and fats. Carbonic anydrase is active in regions which regulate fluids, such as the kidney, the gut, the eye, and the vestibular apparatus of the inner ear.

Carbon dioxide limits the electrical depolarization of nerves and muscles, a phenomenon first discovered by Gilbert Ling. This prevents the over-excitation and exhaustion of brain cells and muscle cells, including the heart. The presence of carbon dioxide limits the formation of lactic acid. This explains the "lactate paradox" of high altitude exertion (lactic acid isn't produced during hypoxic exercise, since carbon dioxide is retained

by the Haldane effect, in which the low oxygen pressure fails to displace all of the carbon dioxide carried in the blood cells), and it explains why lactic acid tends to be always present in the blood in hypothyroidism, diabetes, and obesity—insufficient carbon dioxide is produced, and lactic acid is produced even without oxygen deprivation or stress. This aerobic glycolysis, the production of lactic acid in the presence of oxygen, was defined by Otto Warburg as the characteristic cancer metabolism. The "respiratory defect" in which the Pasteur effect (suppression of lactic acid formation in the presence of oxygen) fails to operate, consists largely of the failure to produce carbon dioxide in the mitochondria.

Simple hyperventilation causes muscle spasms and paresthesia (prickling of the skin), in an experiment anyone can perform in a few minutes. When a large amount of carbon dioxide is blown off, the blood's pH increases very slightly, because of systemic adjustments. The "calcium deficiency" theory of tetany would suggest that increased alkalinity of the blood decreases the "availability" of ionized calcium, and that (somehow) the "decreased availability of ionized calcium" interrupts a relaxed state of the nerves and muscles. At least, that's the explanation that I have heard many times, though I am stating it in a way that makes it sound fairly crazy. (See Stadler, et al., 1995.) But, in fact, everywhere calcium is studied, it is an activator, an excitant, a goad to activity, when it enters the cytoplasm. The evidence is that hyperventilation, which changes the serum concentration of bicarbonate, magnesium, potassium, chloride, and phosphate, does not change the serum calcium concentration, while it does *increase the intracellular calcium content.* (Fujimoto, et al., 1987; Stadler, et al., 1995.)

The combination of the calcium ion, Ca^{2+}, with the bicarbonate ion, HCO_3^-, forms a very soluble complex ion with a single positive charge. In the saliva, there is more carbon dioxide than in the mouth, and this situation is believed to explain the fact that calcium which is dissolved in the saliva tends to be deposited in an insoluble form as it loses its solublizing bicarbonate, and the insoluble form contributes to dental plaque. (Presumably, this physical principle would account for the deposition of calcium in the walls of blood vessels or in any tissue which is relatively deficient in carbon dioxide.) Similarly, when serum bicarbonate decreases, the calcium escapes from its soluble complex, and in effect the available calcium—the forms of calcium which are not bound to bicarbonate--has *increased,* exactly the opposite of what the Carlson school has argued.

Calcium, which is released into the cytoplasm by the excitotoxins, triggers the release of fatty acids, the activation of nerve and muscle, and the release of a variety of transmitter substances, in a cascade of excitatory processes, but at the same time, it tends to impair mitochondrial metabolism, and progressively tends to accumulate in mitochondria, leading to their calcification death, which is also promoted by the antirespiratory effects of the unsaturated fatty acids and the lipid peroxidation they promote. Iron and calcium both tend to accumulate with aging or stress, and both promote excitatory damage; bicarbonate contributes to keeping iron in its inactive state, and probably has a similar effect against a broad spectrum of excitatory substances. Histamine release, nitric oxide, and carbon monoxide are broadly involved in excitotoxic damage, and carbon dioxide tends to be protective against these, too.

Besides the simple excitotoxic killing of nerve cells, the processes which impair carbon dioxide production set in motion the long degenerative process that ranges from diabetic lacticacidemia to dementia. In Alzheimer's disease, brain respiratory metabolism is inhibited, creating a carbon dioxide deficiency with an excess of lactic acid and ammonia. Both Alzheimer's disease and multiple sclerosis involve depressed brain metabolism combined with an inflammatory process. In any inflamed tissue, the enzyme beta-glucuronidase is activated, and this enzyme releases estrogen within the irritated cell, activating another sequence of neurotoxic processes.

In Alzheimer's disease, two other outstanding features are the tangles of microtubular material left where cells have disintegrated, and the amyloid plaques, which often form in

extracellular spaces and around blood vessels. One of the forms of amyloid (amyloid is named for its "starchy" appearance in stained slides) is produced from the normal protein, transthyretin, which carries vitamin A and thyroid hormone, when this protein is "glycosylated," by the addition of sugar molecules. In this glycosylated form, it resembles a mutant protein, and binds to the extracellular matrix. This glycosylation can occur spontaneously and quickly, in the absence of enzymes to catalyze it, when there is too much glucose present, and when the protein's amino groups (usually lysines) are not protected by being combined with carbon dioxide (as carbamino groups). The carbamino groups form rapidly when there is an abundance of carbon dioxide, but also rapidly decompose in the absence of carbon dioxide, allowing the protein to be structurally degraded by the addition of sugar molecules.

Reactions very similar to these occur when the products of lipid peroxidation attach themselves to proteins.

Similar reactions, reflecting metabolic and energetic conditions, can alter the structure and organization of the neurotubules, leading to cell death and the formation of the characteristic neurofibrillary tangles.

W. F. Koch also found that excessive coagulation was produced in the toxic antirespiratory state. Carbon dioxide, probably by controlling the availability of calcium, is an important protection against abnormal clotting. The prevention of clotting by carbon dioxide is thought to be part of the explanation for its protective effect against oxygen deprivation. (Pak and Sverchkova, 1987.) Hyperventilation causes increased vascular permeability, leading to hemoconcentration when a large portion of the blood's water escapes into the tissues. Vascular spasm, increased viscosity of the concentrated blood, and disturbed coagulation processes undoubtedly contribute to a wide range of health problems, including stroke, heart attack, and multiple sclerosis.

Since permanent high altitude residents chronically retain a larger amount of carbon dioxide in their tissue, I have looked for data on the incidence of degenerative brain disease among high altitude populations. In Kashmir, a house-to-house study of more than 66,000 people found that nearly one percent of the population suffered from some neurological impairment, such as cerebral palsy, epilepsy, mental retardation or stroke. But no cases of Alzheimer's disease or multiple sclerosis were found. In India, the incidence of these diseases is much lower than in the U.S., but their *absence* in Kashmir is remarkable.

If excess lactic acid in the brain tissue is characteristic of Alzheimer's disease and multiple sclerosis, then the "lactate paradox" suggests that a slightly higher retention of carbon dioxide in the brain of Kashmir residents would **counteract chronic excitotoxic effects, suppressing the stress metabolism** which leads to the degenerative brain diseases. Experimentally increased carbon dioxide tends to decrease intracellular calcium, and to decrease brain excitability.

Cancer, the classical disease of extreme "aerobic glycolysis," is also negatively associated with increased altitude. Mortality from heart disease, too, decreases with increasing altitude, and the role of carbon dioxide in heart function is very clear.

The neuroprotective steroids, progesterone and pregnenolone, and magnesium and carbon dioxide all protect against excitoxicity and the related excess of intracellular calcium, while promoting normal calcification. The thyroid hormone happens to promote the production of these steroids and carbon dioxide, and the retention of magnesium. By the simple process of avoiding the antithyroid substances, especially the polyunsatured fatty acids, the degenerative processes discussed here will be minimized. Cyanide, another common component of foods (usually in the bound form as cyanogenic glycosides, in seeds, sprouts, nuts, and grains), has specific antagonisms to carbon dioxide, thyroid, and respiration.

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Ray Peat's Newsletter

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Edema, estrogen, and aging: A universal problem, and better therapies

Before talking about the harmful effects of edema, and of the things that cause edema, and of the things that can remedy the various edemas, I think it's necessary to look at a few recent events in the very long history of medicine's intervention in this problem of excessive tissue water. Otherwise, I don't think the great importance of edema, and its fundamentally "estrogenic" nature, will be clear. Aging, shock, hypertension, cancer, heart failure, and many other biological problems involve edema as a central factor, and relieving the edema is probably an essential part of solving those problems.

Carbon dioxide and estrogen are important in the regulation of water, which is a major problem in stress and aging.

Some people have defined "homeostasis" as maintaining a consistency in the things dissolved in the body's water. Physiologists have tried to explain how homeostasis is maintained, but they have had the greatest difficulty with understanding *the water itself,* and the things which allow the body to maintain the right amount of water in the various compartments of the body. ***Edema*** ("an abnormal collection of liquid") isn't a sophisticated concept, and is generally used interchangeably with "water retention" and "swelling."

Many people think of edema as an esthetic problem: They don't like the appearance of fat fingers, swollen ankles, puffy eyelids, and soggy-boggy tissues in other areas. Swollen breasts and uterus can cause pain, and often occur premenstrually along with more generalized water retention. Estrogen's role in edema is understood by many women, but therapies have generally been directed toward the water itself, with empirical diuretics, because edema's *causes* aren't explained in medical texts.

This is, to a great extent, the result of deliberate distortion by the drug industry of the issues involved. Beginning in the 1950s, the sale of new patented diuretics (replacing traditional diuretics) began in an atmosphere in which estrogen was being given to pregnant women, to prevent various complications of pregnancy (which in fact were caused by excessive estrogen). Excess estrogen as the cause of toxemia couldn't be discussed openly, and the diuretics were sold as additional tools for controlling pregnancy-associated water retention, weight gain, high blood pressure, and damage to the fetus. Pregnant women were also told to diet to limit weight gain, and to sharply limit their consumption of salt. Estrogen, diuretics, salt restriction, and dieting were demonstrably all harmful to pregnant women and their babies, but they were imposed by the pharmaceutical-medical establishment. (Besides their appalling promotion of the new diuretics "to prevent toxemia," the pharmaceutical industry presented the new chlorothiazide diuretics as the only drugs capable of correcting the "sodium problem," creating multiple unnecessary confusions.)

Shock, pneumonia, and hypertension are among the consequences of edema.

Understanding edema is essential for understanding stress, for preventing stress-induced sickness, and for resuscitation

Emphasis on diet and sodium restriction served to put the blame for pregnancy problems on the women who couldn't control their

appetites. Besides the medical obscurantism that didn't want to examine estrogen's role in toxemia of pregnancy, there was a mechanical conception of the causes of edema. Although no one could explain how a molecule could fling an atom of sodium out of a cell or across membranes such as the kidney tubules, "sodium pumps" were said to explain the different concentrations of sodium in different compartments, and water was said to passively "follow the sodium." This theory failed to explain how water could be retained while sodium was lost, or why osmotic pressure varied under certain conditions..

Physical chemists understood how water could be moved from one compartment to another, by the process of electro-osmosis, but cell physiologists still generally believe in their sodium pumps and give them responsibility for the distribution of water. Medical textbook discussions of edema have a pitiful-comical quality, because their elaborate Rube Goldberg machines* don't do what they are supposed to do, despite all their embarrassing *ad hoc* devices and convolutions.

Because of the abundance of oxygen in the world, most things are in a relatively oxidized state. Oxygen's name means "source of acid," and it creates acids because of its great affinity for electrons. Acidity is defined as a tendency to *accept electrons, or to release protons.* In water, it is common to speak only about the protons, and to think of acidity as an excess of protons, a low pH. Finely divided minerals such as clays and zeolites, and partly oxidized organic substances, have a strong tendency to absorb and bind water,because of the polar nature they have because of their oxygen content. It is extremely hard to completely dehydrate materials such as proteins and nucleic acids because of their polar, predominantly acidic, affinity for water.

*Rube Goldberg, who was educated as an engineer, described his cartoon machines as "symbols of man's capacity for exerting maximum effort to accomplish minimal results." He said "there are two ways to do things, the simple and the hard way, and a surprisingly large number of people prefer doing things the hard way."

Soluble alkaline materials, with a tendency to *release electrons or accept protons,* associate with the acidic groups, tending to produce a neutral pH. However, extremely water soluble chemicals don't have complete freedom to associate with their oppositely charged groups in materials that are insoluble in water; some enter, some are excluded. This principle can be demonstrated with drops of simple acidic organic liquids suspended in water containing ionized solutes: Their different solubility, combined with their chemical affinities, creates an equilibrium, in which the organic droplet has a negative electrical charge.

Dead cells, such as hair, behave in this way too, because this electrical and ionic behavior is normal for any acidic solid, or immiscible liquid phase. It is the failure to recognize ordinary physics and chemistry that has made Rube Goldbergian cell physiology seem plausible to so many people. Bioelectricity, and ionic selectivity, are fundamentally passive, near-equilibrium processes, that don't require any convoluted "special" apparatuses to explain them.

When oxidative metabolism enters the picture, new acids are being formed inside cells. Carbon dioxide formation is the essence of oxidative metabolism, along with the formation of metabolic water, from the interactions of carbon fuel, electrons, and oxygen. Even before carbon dioxide has covalently reacted with water, to form carbonic acid, it has a great affinity for electrons. This affinity, which predisposes it to react with water and amines, governs its non-covalent, adsorptive properties, but these are passed over by most physiologists. Carbon dioxide is chemically active in many ways, besides its contributions to bicarbonates and carbonates and carbamates and organic acids.

Both spontaneously, and enzymically, carbon dioxide combines with water. Formed inside the respiring cell, it is constantly leaving the cell as carbonic acid, bicarbonates, and carbonates. As it streams out of the cell, any positively charged group, such as a calcium ion, that it takes along will enter extracellular fluids with the carbonate or bicarbonate ion, approximately as a pair with equal positive and negative charges, but the removal of the alkaline metal ion will tend to restore the proteins' acidic nature, which had been

Acidity: accept electrons or libir protons

approximately neutralized by the passive interaction of acids and alkalis. The proteins, and the cells, will be electrically charged to a higher degree by respiration; nerve cells will show a voltage of about a tenth of a volt, while red blood cells, that don't produce energy by respiration, show an electrical potential of less than 1/400 of a volt. **This is partly a mnemonic device for visualizing the general scheme in which equilibrium conditions interact with dynamic metabolic processes.** The adsorptive effects of carbon dioxide, and a great variety of other chemical effects, modulate the cell's structure and function so that it retains far more potassium than sodium, and is able to excrete calcium while binding magnesium. But this simplified picture of carbon dioxide's effects on minerals makes it possible to understand the fact that the blood's pH is higher than the cell's, and many other mysteries, without resort to special hypothetical devices. The alkaline metals that have been mobilized from respiring cells in association with carbonic acid remain alone in the blood when carbonic acid turns into gaseous carbon dioxide and leaves the blood in the lungs. Protons, if we have to talk about them, are left in the cells, and subtracted from the blood, by the reactions of carbon dioxide, but the conventions for talking about the blood's alkalinity relative to the cells omit the background conditons: The intrinsic acidity of the cell substance, and forces exerted by the cell substance on the dissolved substances.

Myxedema, or mucous-edema, is a classical feature of hypothyroidism, but it's not always noticed, because it can occur in different tissues to different degrees. The protein that forms the mucoid jelly is partly made up of ordinary blood proteins, including albumin; transthyretin, the protein that carries thyroid hormone and vitamin A, is sometimes increased, and some connective tissue glycoproteins contribute to its bulk. Similarly to the way that mucus protects the lining of the intestine from irritants, there is probably a protective aspect to the accumulation of myxedema in stressed tissues, where it has a cushioning effect.

Starting with either hypothyroidism or hyperestrogenism, or both, since they tend to occur together, there are many pathways that lead to the excessive accumulation of water in tissues. In hypothyroidism, the adrenergic nervous system tends to overactive, and adrenalin production is sustained at a high level even when there isn't any external reason for it, since it is needed to maintain adequate blood sugar and energy, in the inefficient metabolic state of hypothyroidism.

Adrenalin mobilizes free fatty acids from tissues, including fat and muscle tissues. Estrogen itself produces elevated free fatty acids. When the free fatty acids are unsaturated, they cause edema, by making blood vessels leaky, and by making cells take up extra water; this can cause brain swelling, stiffening of the heart muscle, and thickening of the lining of blood vessels, eventually obstructing them.

Hypothyroidism suppresses respiration as a source of energy, so little carbon dioxide is produced, and lactic acid is formed even when there is no noticeable stress. This in itself resembles hyperventilation, since loss of carbon dioxide is the defining feature of hyperventilation, but the presence of abnormally high adrenergic activity, and of free fatty acids, stimulates further hyperventilation, exacerbating the loss of carbon dioxide. Decreasing the carbon dioxide impairs respiration even more, leading to increased lactic acid production, and that stimulates more adrenergic activity, and so on, in a vicious circle. Unsaturated fats also suppress respiratory production of carbon dioxide, and block the entry of glucose into cells.

Estrogen excess suppresses the liver's ability to synthesize albumin, and when this is combined with the leakage of albumin into the tissues (where it is slowly destroyed) and into the urine, the blood loses its ability to retain sodium, much of which is associated with albumin. Carbon dioxide, some of which is produced in the kidneys, helps to retain sodium, and this is probably the reason that hypothyroid people have difficulty retaining a normal amount of sodium (producing *hyponatremia*).

Both animal and human studies have shown that estrogen lowers the osmolarity of the serum and other body fluids, creating a more "diluted"

liquid. Some evidence suggests that it acts at different points to decrease the sodium (and albumin) in the blood, and to allow it to enter tissue cells, or to be lost in the intestine or urine. Although this dilutional effect of estrogen on the blood is small, it certainly increases the tendency of water to enter cells. Especially when combined with lactic acid and unsaturated fatty acids,

Since a hypotonic solution imitates the effects of estrogen, and things that cause tissue leakiness, such as cholera toxin, act like estrogen in the uterus, the edema itself produced by estrogen seems to be a central part of its normal physiological action. Histamine and serotonin and other inflammatory factors released by estrogen are known to contribute to its ability to produce edema. The excess nitric oxide produced under the influence of estrogen probably contributes to some edematous, inflammatory, and degenerative conditions. Since these effects of estrogen on tissue water are considered to be nongenomic, and independent to some extent of the normal estrogen receptors and response elements, any tissue is probably susceptible to estrogen-induced swelling, as well as to the swelling produced by unsaturated fats and carbon dioxide deficiency. Part of the toxicity of unsaturated fats could be their requirement of energy to be oxidized (S. Clejan and H. Schulz, 1986), but they reduce the efficiency of energy production in a variety of other ways.. In shock (whatever the cause), tissues become edematous, as water moves out of the blood stream. The weight of organs increases tremendously as a result of shock. In severe stress. shock, and estrogen poisoning, the production of energy is impaired by the swelling itself, though it may have been low energy production that allowed the shock-state to develop.

If estrogen can cause edema in any tissue, then antiestrogens, such as progesterone, can probably protect against stress in any tissue.

In the premenstrual syndrome, as in pregnancy, a progesterone deficiency can cause generalized edema. Tom Brewer, who founded the Society for the Protection of the Unborn through Nutrition, and S. Shanklin and J. Hodin, in *Maternal Nutrition and Child Health,* argued that salt restriction, expecially when combined with diuretics and a diet without adequate protein, caused exaggerated edema in pregnancy, producing a great risk of hypertension by reducing the blood volume needed for adequate perfusion of the kidneys, and damaged the development of the fetus, because of inadequate blood perfusion of the uterus and placenta.

After I was convinced of the manner in which salt restriction could cause edema, and knowing that women are told to restrict salt to prevent premenstrual edema, I began suggesting that women salt their food to taste, increasing their salt consumption premenstrually if they craved it. I had never known of salt restriction to prevent premenstrual edema, but I immediately began hearing that the women who ate all the salt they wanted no longer experienced premenstrual edema.

After a couple of years, I was satisfied that adequate protein and salt consistently prevented premenstrual edema. I read an article by some people who noticed that their patients who were on low sodium diets "for high blood pressure" very often developed insomnia. They knew that sodium restriction raised adrenalin levels, so they took their patients off the low sodium diet, and cured their insomnia.

Since I had become a sound sleeper as soon as I began taking thyroid, and had seen that thyroid alone would cure most people's insomnia (sometimes, as one doctor described his experience, "better than morphine") I began to understand that the adrenalin which disturbed sleep was an indicator of defective energy production, and that the things which restored sleep—thyroid, salt, sugar, protein, and progesterone, for example—were acting directly on the cells' energy production.

Since elevated adrenalin tends to raise blood pressure, I began explaining the effects of salt and thyroid to friends who were over 80. They found that they slept better, had more regular heartbeats, and didn't suffer from swollen feet when they ate a normal amount of salt. It didn't cause their blood pressure to rise.

Sodium bicarbonate and sodium chloride are known to have diuretic action; sodium

bicarbonate is often used to treat poisoning, to accelerate elimination of the toxin, for example.

Although there are complex theories about their effects, I suspect that two main processes are involved. By increasing the osmolarity of the blood, the blood volume is expanded by the entry of water from the tissues, and this increased perfusion of the kidneys would increase the formaton of urine, and, secondly, their increased concentration might simply increase the energy production of the kidneys. **The kidneys normally have a high oxygen consumption and an unusually high carbon dioxide concentration, which participates in the formation of urine. Acetazolamide, an inhibitor of the enzyme carbonic anydrase, is known to increase the body's retention of carbon dioxide,** and is sometimes used to increase the formation of urine, though its more important uses are in the prevention of edema of the lungs and brain in "mountain sickness" (a result of hyperventilation), and to reduce swelling of the eyes in glaucoma. It is also used to prevent sleep apnea, by correcting the alkalosis that causes it. The inhibition of carbonic anhydrase causes carbon dioxide retention, and this can produce acidosis. Intracellular acidosis has many important cell-protecting effects. By reducing the ionization of the cell's macromolecules, the cell's affinity for water is decreased.

Sodium bicarbonate is a more active diuretic than sodium chloride. I think this has to do with carbon dioxide's special properties, including its relative lipophilicity (preferential solubility in oils or cells), and its chemical combination with water.

Since salt restriction is the commonest way to try to correct edema, it's important to think about the physiological reasoning and evidence that support that common practice. In physiology lab classes, professors sometimes have one group of students drink a quart of ordinary water at the beginning of the class, while another group drinks a quart of isotonic saline (containing roughly a rounded teaspoonful of salt). Everyone measures their urine output over the next few hours, and by the end of the class, it turns out that those who drank the plain water produced about a quart more urine than those who drank the slightly salty water. The conclusion is obvious: For every 9 grams of salt, we retain a quart of water. That's an unfortunate experiment, though, because it creates such a clear impression of salt's immediate effect, but provides no information at all about its longer-range effects. Recently, a British physician, from Mongolia or northern China, studied the incidence of hypertension in her native region, where people consume at least 30 grams of salt per day. She found no hypertension at all, even among the oldest people. In my experiments, it has taken the body only two or three days to adjust completely to a massive change in salt consumption. Many hormones adjust quickly to retain or release sodium, according to the amount consumed, if the person is otherwise well nourished. Hypothyroid people, however, are unable to maintain a normal sodium concentration in their body fluids even when they increase their salt consumption.

Thyroid, protein, sodium, and magnesium will correct most edemas. Progesterone, acting on mitochondria to increase respiratory efficiency, and on structural proteins to change their ionic affinities, synergizes with the other natural factors to correct permeability and water regulation. One of the first people I saw use progesterone was a woman who (after being studied at the Mayo Clinic and many other places) believed she had Bright's disease, and habitually produced an extremely small quantity of urine. A few hours after taking just a few milligrams of progesterone, she telephoned to report that she "had to stop at every gas station on the way home," because she was forming urine at such a great rate. Increased perfusion of the kidneys is one of progesterone's normal functions, that accounts for its ability to prevent or cure "toxemia" of pregnancy. Besides its ability to increase blood perfusion of the kidneys (and other organs), progesterone has an important role in mineral regulation, since it acts as a "weak aldosterone," protecting against both a deficiency and an excess of that adrenal hormone. (The kallikrein enzymes which produce kinins and related hormones are probably involved in the effects of progesterone, estrogen, fatty acids, etc., on the permeability of blood vessels, blood

pressure, swelling, etc., but researchers have surprisingly little interest in that system..)

Brain edema causes seizures, lung edema causes "respiratory distress syndrome," and is a factor in pulmonary hypertension. In the heart and blood vessels, it increases rigidity and decreases the efficiency of blood circulatoin. Degenerative nerve and muscle diseases often begin with edema; degenerative spinal disks, and lens cataracts, are produced by an excess of water.

Although estrogen increases during acute sickness in both men and women, women have a higher incidence of estrogen-related diseases than men do. In spite of a large number of degenerative diseases caused by estrogen, women live significantly longer than men do, and both animal and human studies have shown that it is probably progesterone which gives women this advantage.

It is this female longevity that has allowed the drug companies to suggest that estrogen can prevent degenerative diseases. Estrogen's known promotion of clotting diseases, edema, diabetes, liver disease and blood pressure abnormalities, are ignored while cholesterol is emphasized as a "risk factor" that is favorably influenced by estrogen. Estrogen's elevation of free fatty acids, and the edema produced by these, are ignored as if they had no significance in the degenerative diseases.

I have already written about estrogen's contributions to brain aging and blood clotting diseases, but I plan to write soon about progesterone and thyroid as the important "heart protective" hormones.

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Ray Peat's Newsletter

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Prostate Cancer

It was noticed several decades ago that estrogen causes the prostate gland to enlarge in experimental animals, but by then an oversimplified view of the sex hormones was already well established, that led people to say that "estrogen causes the female organs to grow, and testosterone causes the male organs to grow." Logically extending this mistaken idea led many of the same people to suppose that the "hormones of one sex would inhibit the growth of the reproductive organs of the other sex."

When a friend of mine was told he had prostate cancer, though he had had no symptoms, and should receive large doses of estrogen, I reviewed the literature, to see whether his doctor might have seen something I had neglected. Since that time, I have found it necessary to use quotation marks around the phrases "medical research" and "medical science," because there is a certain kind of "research" performed within the medical profession which is peculiar to that profession.

When I read through the studies cited by the current articles as the basis for using estrogen to treat prostate cancer, I saw that the decisive "research" had consisted of mailing a questionnaire to physicians asking them if they thought it was reasonable to administer estrogen to these patients on the basis of its opposition to testosterone, which was considered to be responsible for the growth of the prostate gland. Many physicians answered the questionnaire affirmatively.

If the questioner's purpose was to determine his legal status in using a treatment, his research method was appropriate, to see whether the treatment seemed reasonable to others in the profession. Legally, a physician is safe if he can count on others to testify that his practice is standard. Unfortunately, for generations his study of the opinions of his peers became the "evidence" of the value of the estrogen treatment. Phrases such as "it is indicated," "treatment of choice," and "standard practice" are used in medicine, as part of the pseudo-scientific mystique of the profession. Physicans who attempt to base their practice on methods that have a sound scientific basis are likely to find that they are violating the norms of their profession.

More than 25 years ago, when I started pointing out that deliberate misrepresentation had been involved in the continued designation of estrogen as "the female hormone," used as a basis for "hormone replacement therapies," I saw that it was hard for people to sustain a critical attitude toward language. Language is prior to judgment, law, science, reason. Those who define the terms set the rules.

> **"...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistenly induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion."** ***Shuk-mei Ho and M. Yu, in "Selective increase in type II estrogen-binding sites in the dysplastic dorsolateral prostates of Noble rats," Cancer Research 53, 528-532, 1993.***

By the mid-1980s, some studies had shown that estrogen treatment didn't prolong the survival of prostate cancer patients at all, but it was argued that the patients who received estrogen were happier than those who didn't.

Apparently, many physicians who were experts in conventional cancer treatment hadn't been impressed by the happiness of their patients

who were receiving estrogen, because a survey at a conference of physicians found that many of them would choose to have no treatment if they learned they had prostate cancer. And more recently, there have been recommendations that older patients shouldn't be treated aggressively, because their cancers are usually so slow growing that they are likely to die of something else related to old age.

In spite of the articles I showed my friend, and my warning that estrogen can cause strokes and heart attacks, he decided to take the estrogen treatment. Within a few days he began suffering from asthma and disturbed sleep. Then he had a series of strokes and died.

Since it was known that estrogen treatment was dangerous for men, and that it increases blood clotting and vascular spasms, there had to be some overriding belief that led to its general use in treating prostate cancer. That belief seems to be that "estrogen, the female hormone, opposes testosterone, the male hormone, which is responsible for the growth--and therefore for the cancerization--of the prostate gland." Everything is wrong with that sentence, but you can find every part of the belief present and functioning in the medical literature. Just to give some context to the association of growth and cancerization, I should mention that Otto Warburg observed that all of the carcinogenic factors he studied caused *tissue atrophy before cancer* appeared. Another important contextual point is that every hormone does *many* things, and every endocrine gland produces multiple hormones.

Since the time of Brown-Sequard and Eugen Steinach, it has been accepted that declining testicular function is a common feature of aging, and testosterone was probably the first hormone that was clearly found to decrease consistently with aging. (Vermeulen, et al., 1972, 1979.)

It has seemed odd to many people that enlargement of the prostate should occur mainly in older men, if testosterone is the hormone that causes its growth, and estrogen is antagonistic to its growth. The nature of the growth of the old man's prostate is very different from its natural growth in youth.

It was also recognized decades ago that estrogen rises in men during old age (Pirke and Doerr, 1975), as it rises in stress, disease, malnutrition, and hypothyroidism (which are also associated with old age). Estrogen is produced in fat (Siiteri, and MacDonald, 1973, Vermeulen, 1976) which tends to increase with age, when thyroid and progesterone are deficient. The conversion of testosterone to estrogen occurs in the testicle itself, but this conversion is also inhibited by the favorable hormonal environment of youth. The active thyroid hormone, T_3, declines with aging, and this necessarily lowers production of pregnenolone and progesterone. Increasingly, in both sexes, it appears that DHEA may rise during stress as a result of a deficiency of thyroid, progesterone, and pregnenolone.

In 1786, John Hunter reported that castration causes a decrease in the size of the prostate gland, and by the end of the 19th century castration was being advocated for treating enlargement of the prostate. In aging men, the prostate gland (both central and peripheral zones) atrophies, and it is within the atrophic gland that cancer cells can be found. Nodular, noncancerous enlargement may occur, with or without cancer. In 1935, an autopsy study showed carcinoma in the prostates of 30% of men by the age of 50. Proliferation of ductal and epithelial tissue is closely associated with prostate cancer, a situation similar to that of the cancerous or precancerous breast. (Simpson, et al., 1982; Wellings, et al., 1975; Jensen, et al., 1976.) The high probability of "epitheliosis" in association with cancer was seen in women in their early 40s, and in women over 60. (Simpson, et al.) (Epitheliosis just refers to an exaggerated proliferation of epithelial cells, the cells covering all surfaces, including the lining of glands, and things as simple as irritation and vitamin A deficiency can cause these cells to proliferate.) In the breast, the proliferative epitheliosis is clearly caused by estrogenic stimulation. The antagonism between estrogen and vitamin A in controlling epithelial proliferation (and possibly other cell types: Boettger-Tong and Stancel, 1995) is clear wherever it has been tested; vitamin A restrains epithelial proliferation. (Wherever estrogen is a factor in the development of

En vieilli le ratio estro/antiestro ↑

abnormal tissue, vitamin A supplementation would seem beneficial.)

In aging women and men, as the breasts and prostate atrophy, their estrogen/antiestrogen ratio increases.

In men with prostate cancer, the fluid secreted by the prostate contains significantly more estradiol than the fluid from men without cancer (Rose, et al., 1984). This is analogous to observations made in women with breast cancer.

The pituitary hormones have diverse functons, including effects on epithelial tissues, other than their "classical" functions. Growth hormone, ACTH (Lostroh and Li, 1957), and ACTH with prolactin (Tullner, 1963) stimulate prostate growth. Prolactin--which is increased by estrogen--stimulates growth of the rat's lateral prostate (Holland and Lee, 1980), and stimulates the growth of human prostate epithelial cells *in vitro* (Syms, et al., 1985). LH (luteinizing hormone) increases when progesterone or testosterone is deficient, and growth hormone and prolactin (which are closely associated in evolution) both increase under a variety of stressful situations, and with estrogenic stimulation. **Prostate cancer patients who had higher levels of LH and *lower testosterone* died most quickly. (Harper, et al., 1984.) Also, a *high ratio of testosterone to estradiol or of testosterone to prolactin* corresponded to better survival (Rannikko, et al., 1981.) Considered separately, patients with *higher testosterone levels had a better prognosis* than those with lower levels, and patients with lower growth hormone levels did better than those with higher growth hormone levels. (Wilson, et al., 1985.)** Has anyone ever tried testosterone therapy for prostate cancer? Or, more practically, a generalized antiestrogenic therapy, using thyroid, progesterone, and pregnenolone? Other drugs (naloxone, bromocriptine, gonadotropin-releasing hormone agonists, and anti-growth hormone druges, e.g.) are available to regulate the pituitary hormones, and might be useful therapeutically or preventively. (See Blaakaer, et al., 1995.) Biskind and Biskind's work (1944) with ovarian tumors might be relevant to both testicular and prostate cancer.

Abnormal patterns of pituitary hormones reflect stress and hormonal imbalance, but they are also directly involved in widespread changes in tissue content of glycoproteins. The prostate is specialized to secrete large amounts of mucin. The endocrine physiology of prostate mucin secretion is poorly understood, but it is likely that there are interactions between growth-regulatory and secretion-regulatory systems.

In recent years, prostate cancer has been one of the fastest increasing kinds of cancer, and it isn't apparent that increased treatment has had an effect in lowering the death rate. The postwar baby-boom (following the baby-bust of the great depression) created an abnormal age-structure of the population, that has been used to argue that the war against cancer is being won. Increasing environmental estrogens are known to cause many reproductive abnormalities, and their contribution to prostate cancer would get more attention if estrogen's role in prostate disease were better known. Environmental estrogens are clearly responsible for genital deformities and sterility in many species of wild animals, but when the causal link is made between estrogens and human abnormalities, the estrogen industry sends its shills in to create controversy and confusion. Even the effects of estrogens in sewage, known for decades, are treated as State Secrets: "There had been reports of hermaphroditic fishes in one or two rivers, and government investigators had been studying them since the late 1970s. **But no one had been aware of the work because it was classified."** (Lutz, 1996.)

Testicular cancer is easy to diagnose, and its incidence has clearly increased (100% in white men, 200% in black men) since 1950. Undescended testicles, urethral abnormalities, etc., similar to those seen in DES sons and in wild animals, have also increased. So the tremendous increase in the death rate from prostate cancer during the same time has a meaningful context.

Although the animal studies showed that estrogen treatment promotes enlargement of the prostate, it was possible to suppose that the human prostate's growth might be stimulated only by testosterone, until tests were done *in vitro* to

GH + Prolactine + ACTH stimule la croissance de la Prostate

↑ sont ↑ par stress et estro. Si ↑ testo : estra ou testo : Prola c'est Bon

Testo ne stimule pas la ÷ cellulaire mais Insu et Prolac oui

determine the effects of hormones on cell division.

In human prostate slices, several hormones (including insulin, and probably prolactin) stimulated cell division; **testosterone did not,** under these experimental conditions. (McKeehan, et al., 1984.) Contrary to the stereotyped ideas, there are suggestions that supplementary androgens could control prostate cancer (Umekita, et al., 1996), and that antagonists to prolactin and estrogen might be appropriately used in hormonal therapy (for example, Wennbo, et al., 1997; Lane, et al., 1997).

By the age of 50, men often show an excess of both prolactin and estrogen, and a deficiency of thyroid and testosterone. This is the age at which enlargement of the prostate often becomes noticeable.

Estrogen's role in prostate growth and cancerization is clear: "...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistenly induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion." (Ho and Yu.)

Progesterone and pregnenolone also decline in aging men. Several studies using synthetic progestins have shown that they effectively shrink the hypertrophic prostate, and the saw palmetto remedy for prostate enlargement has been reported to contain pregnenolone, or something similar to it. These materials might be expected to reduce conversion of testosterone or other androgens to estrogen.

The prostaglandins were discovered in prostatic fluid, where they occur in significant concentrations. They are so deeply involved with the development of cancers of all sorts that aspirin and other prostaglandin inhibitors should be considered as a basic part of cancer therapy. The prostaglandins have local and systemic effects that promote cancer growth. ("The prostaglandins and related eicosanoids synthesized from polyunsaturated fatty acid precursors have been implicated as modulators of **tumor metastasis, host immunoregulation, tumor promotion, and cell proliferation."** Hubbard, et al., 1988.)

Estrogens cause elevation of free fatty acids, and there are many interactions between the unsaturated fatty acids and estrogen, including their metabolism to prostaglandins, and their peroxidation. Estrogen's roles as free-radical promoter, DNA toxin, carcinogen, tumor promotor, modifier of tissue growth factors, anti-thymic hormone, etc., as well as its local effects on the prostate gland, have to be kept in mind. Most of the interest in studying estrogen's contributions to prostate cancer relates to the existence of estrogen receptors in various parts of the prostate. While that is interesting, it tends to distract attention from the fact that many of estrogen's most important actions don't involve the "receptors." A **direct excitatory** action on prostate cells, and **indirect** actions by way of the pituitary, pancreas, thyroid, adrenal, fatty acids, prostaglandins, histamine and circulation are probably essential parts of the cancerization process.

The unsaturated fatty acids, but not the saturated fatty acids, free estrogen from the serum proteins that bind it, and increase its availability and activity in tissue cells.

Thyroid supplementation, adequate animal protein, trace minerals, and vitamin A are the first things to consider in the prevention of prostate hypertrophy and cancer. Nutritional and endocrine support can be combined with rational anticancer treatments, since there is really no sharp line between different approaches that are aimed at achieving endocrine and immunological balance, without harming anything.

Avoiding tissue atrophy is very closely related to promoting healthy regeneration. These processes require efficient energy production, and an appropriate balance between stimulation and resources. Growth hormone is sometimes recommend to correct tissue atrophy, but the evidence seems reasonably clear that it is a factor in the promotion of tumefaction of the prostate. The only study I have seen suggesting that it might be beneficial in prostatic cancer was a 14 day experiment done in female rats. Numerous publications suggest that blocking growth hormone is

Aging = ↓ THY, ↓ Preg, ↑ estro : ↑ testo en estro dans Testi, ↑ stress qui ↑
GH, Prolac, insuline, ACTH et eux ↑ ÷ cellulaire un supp de THY, Preg, A, Protéine cest bon

beneficial in treating prostate cancer; in future newsletters I will be discussing the evidence that growth hormone, like estrogen, cortisol, and unsaturated fats, tends to promote degenerative changes of aging.

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Ray Peat's Newsletter

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Hayflickers, Dolly & dandruff: The "telomeric clock" is not a valid theory of aging.

The roles of nutrition, estrogen, and progesterone in stress-related energy problems: A meaningful pattern for all organisms.

I. Introduction

Besides the commercially promoted idea that melatonin has something to do with a "biological clock," there are two main doctrines among biologists about the nature of the clock that they suppose exists. One group argues that a group of brain cells called the suprachiasmatic nucleus has a regular rate of firing that is "determined by genes" and that controls biological rhythms. Unfortunately for that theory, the firing rate of those cells turns out to be variable under different conditions of metabolism and temperature (Ruby and Heller, 1996).

"Estrogen's identity as a shock-hormone gives an insight into the context-dependent aging of cells and carcinogenesis. The pro-respiratory progesterone is involved as estrogen's antagonist at the deepest molecular levels."

Another general kind of clock is proposed to be "determined by the genes," or genetically "programmed," and in this case the clock is supposed to determine how long an animal can live.

Neither of these groups has even tried to dispose of the facts that have accumulated over several decades suggesting that there is no independent biological clock at all, but rather an ability of cells and organisms to perceive rhythmic environmental conditions. Frank A. Brown, Jr. (Univ. of Indiana) and Alexandre Rothen (Rockefeller Univ.) devised many experiments that clearly demonstrated that biochemical, metabolic and physiological rhythms are responsive to cues other than light and darkness. The geomagnetic field is one type of cue that has demonstrable biological effects.

The doctrine of a genetic clock causing aging denies the role of environmental factors in the aging process. Cigarette companies argued that "we *don't know* the cause of cancer, so go ahead and smoke." The genetic clock people claim to *know* the cause of aging, and that it is not environmental factors.

"The stem cell is defined as that cell in a tissue which, under normal circumstances, maintainsits own population, undiminished in function and size, and furnishes daughters to provide new functional cells of that tissue.The daughters may, or may not, have to undergo further differentiation and/or maturation in order to achieve their functional stage. The fundamental characteristic of a stem cell, therefore, is self-renewal. Evidence is presented which implicates the microenvironment as a major component of the stem cell system, without which stem cells cannot be maintained. Furthermore, it is suggested that stem cell properties do not reside in one specific cell type in the population but, when necessary, cells other than those normally playing the stem cell role, can have stem cell function imposed upon them by the appropriate microenvironment. The stem cell "niche" hypothesis is presented to explain the dependence of stem cells upon their microenvironment. The postulate is offered that there are no cells which are intrinsically stem cells but that a range of cells in a tissue possess stem cell potential to a greater or lesser extent." "The stem cell system," R. Schofield, Biomed Pharmacother, 1983, 37:8, 375-80.

can live much longer than the animal they came from, and that the age of the donor doesn't determine the survival of the transplant.

Studies of the rate of cell division in the lining of the intestine and of the bone marrow cells that continuously produce red blood cells throughout the life-span also have shown gross violations of the "Hayflick limit." Dandruff, the result of the steady division of cells in the epidermis, and the growth of nails and hair, are easily visible demonstrations that Hayflick's observations were just the result of the special conditions he created in his cell culture bottles.

The gradual accumulation of support for the principles Carrel outlined includes evidence that cell-to-cell interactions (R. Auerbach, 1972), adequacy of glucose supply, oxygen and carbon dioxide, appropriate pH, osmolarity, hormones, extracellular matrix (Gospodarowicz), hormones, and many regulatory substances including proteins and fats, **can fundamentally change the ability of cells to divide in culture vessels.**

For example, Gospodarowicz, et al. (1983) found that growing cells on "extracellular matrix," and with some natural substances from serum, rather than on plastic, made the difference between an *in vitro* longevity of 15 or 24 divisions, and "at least 88" cell divisions.

If the "intrinsic cell aging" people want to talk in terms of "programming," then we would have to say that cells are constantly open to "reprogramming," which is to say that they are perceptive and responsive to their environment.

Hayflick's method began with tissue that could be kept, either at room temperature or at 5 degrees, "for at least 5 days" (and "up to 3 weeks") "without apparent loss of viability." Although lactic acid production is a sign of stress, it seems that Hayflick took it as an indication of life: "Once the cultures have become confluent cell sheets, the cells are very active metabolically, as shown by the fact that the GM [growth medium] becomes acid faster than in cultures of heteroploid cell lines inoculated with the same number of cells." "Although mitotic activity eventually ceases in the culture, acid production continues; and as dictated by drops in the pH, cultures can be fed for a few months until all acid production ceases and the culture is observed to have completely degenerated." Among the ridiculously antiphysiological conditions used in Haflick's experiments was the addition of high concentrations of penicillin and streptomycin, or aureomycin, to the growth medium. (See Pershadang, et al., 1982.) He refers to Carrel's techniques as "primitive," and says "In any event, Carrel's experiment has never been confirmed." (Carrel's experiment continued for 35 years, so it will be a while before anyone repeats it.) **Carrel's "primitive" method involved frequent addition of chick embryo extract** rather than Hayflick's commercial solutions of salts, buffers, and antibiotics, with the addition of very small amounts of calf or horse serum. Using fluids from the same species, from an embryo rather than from an adult, and avoiding harmful additives, might be more properly called a sophisticated technique, rather than primitive incompetence. (Smith, et al., 1985, showed that DNA "repair capacity was always found to be greatest in medium supplemented with autologous plasma.")

The essence of the telomeric clock doctrine is that the telomere shortens with aging, making cell division impossible, and causing the organism to suffer the symptoms of aging, while the "immortal germ cells and cancer cells" have active telomerase that allows them to maintain long telomeres. Besides the "inappropriate" telomere length that has been seen in some individuals of different ages, there are so many exceptions to the rule that it is inaccurate to speak of a rule.

Mice, with a very short life-span, have active telomerase in their body tissues, while people normally don't. Telomerase isn't needed to form or maintain telomeres. Some cancers have long telomeres, some don't. Telomere length varies between organs in the same animal, and even between chromosomes in the same cell.

To say that the theory of the telomeric-mitotic clock is complete junk is not to question the importance of the telomere itself--like any part of the cell, it is complex, important, and interesting.

La cell n'est pas limitée et dépend de l'on glucose, Dioxide de C., pH, hormone, macro, micro et peu se reprogrammer par rapport à son environnement

IV. DNA, stress, and estrogen

If Hayflick and Carrel have anything in common, it is the observation that aging is closely associated with the slowing of cell division.

Carrel's observation that the rate of healing is slower in old individuals has been repeated in different systems, for example (Lambert, et al., 1979) **showing that DNA repair synthesis is retarded in cells from old people. Estrogen also slows DNA repair** (O'Brien, 1993), as well as causing increased DNA breakage.

Estrogen's identity as a shock-hormone gives an insight into the context-dependent aging of cells and carcinogenesis. The pro-respiratory progesterone is involved as estrogen's antagonist at the deepest molecular levels.

Fifty years ago, estrogen was shown to imitate all of the physiological features of the shock phase of the stress reaction, and later it was found that histamine and estrogen (and now, nitric oxide) have parallel shock-promoting actions.

More recently, cells (all kinds of cell, including bacteria) have been found to have a system of proteins, called heat shock proteins, that are produced in response to any stress or shock, and estrogen turns out to have a very close association with these stress-induced proteins. Estrogen induces the heat shock proteins, and the heat shock proteins activate or **stabilize the estrogen receptor, so that injury in general facilitates the action of estrogen on the cell.** Progesterone and its receptor have an opposite and antagonistic effect on the heat shock proteins.

In 1970, my proposal that the estrogenic state and the senescent state were very closely related seemed strange to people who had heard estrogen treatment promoted as the way to prolong youth and to stay "forever feminine," but a few years after I had finished my dissertation, Terry Parkening, who had worked in Proferssor Soderwall's lab at the same time I had, began publishing observations of elevated estrogen levels in a variety of aging animals. Estrogen is now known to increase with athletic stress, trauma, sickness, endotoxin poisoning, etc., and to be an essential factor in prostate cancer, as well as in essentially all other cancers, so it doesn't seem to be such a big step to go from "stress hormone" to "age hormone." Estrogen is beginning to lose its false identity as the "female hormone," which was always just a promotional concept of the pharmaceutical industry. Hundreds of false claims have been made about estrogen's "youth promoting" effects, but they always turn out to be the opposite of what is claimed. For example, "estrogen increases the collagen content of skin," but in fact collagen accumulation is characteristic of aging, radiation injury, and many other types of damage. "Estrogen makes the skin plumper," but it is by causing water retention; bloating might stretch wrinkly skin until it is smooth, or even tight, but a swollen old face is, if anything, biologically older than a lean and creased face. (I have discussed many other such advertising ploys in my books, e.g., *From PMS to Menopause: Hormones in Context.*)

The types of adaptation to stress that are known to occur both *in vitro* and in normal aging of the animal, include the various defensive systems such as the heat shock proteins, which are induced by stresses that interfere with the cell's energy supply.

During the last 35 years there have been many demonstrations that cells in culture do not get an optimal amount of oxygen. (Wolffe, et al., 1984, for example.) Kondo et al. (1997) have recently shown that cells grown at the interface where the culture medium meets the air are more like normal cells: They "possess highly differentiated functions and structures compared with the cells cultured under immersion." Previously, as Warburg pointed out, it was found that the cells that grow in a sheet on the bottom of the vessel were much more oxygen-deprived than the cells which are immersed, but suspended, and receive oxygen and nutrients from all sides.

Suffocation and x-ray injury produce an estrogen-like response in animals. The oxygen deprivation in tissue culture, which Warburg showed created the characteristic cancer metabolism, produces the pro-estrogenic heat shock proteins, as well as other stress substances. The antagonism of progesterone to the actions of this heat stress system gives us

Stress ↑ Heme oxygenase (Protéine) level ↑ Carbon monoxide et leur ↑ métabo du cancer
métabo du cancer = glycolyse aérobie avec acide-Lactique : Pas normal car O2 est là

further insight into how to redirect cells away from the stress pathway.

During oxidative stress, a variety of stress proteins are produced, besides the heat shock system. Heme oxygenase, which produces carbon monoxide, is one of these stress proteins, and I have previously discussed how this stress-induced production of carbon monoxide could stabilize the cells' dedifferentiated tumor-producing state, since carbon monoxide produces what Warburg has characterized as the "cancer metabolism," aerobic glycolysis, in which cells produce lactic acid even in the presence of oxygen. In Hayflick's original article (Hayflick and Moorhead, 1961), the production of lactic acid by the cells doesn't seem to be of interest to the authors. I have also introduced the idea that the stress-proteins could have far reaching effects through an effect on the structure of water.

But apart from those points, it is now well established that the heat shock proteins stabilize and reinforce the effects of estrogen. Estrogen tends to shift cells away from differentiated functioning and toward simple cell division, a sort of dedifferentiation. This cell division is important for reproduction, and it is also part of a basic process of tissue regeneration. **During stress or injury, as well as in normal growth, cells have to make the basic decision of whether to grow or to die in the non-inflammatory process called apoptosis, or to differentiate and contribute to the functional systems of the organism.** The heat shock/estrogen system protects cells against "altruistic cell death," but ordinarily the organism rescues the cells from that dedifferentiated state by providing energy, oxygen, and signals to restore them to an appropriate functional state.

The stress pathway at first stimulates cell division, directing cells to differentiate down a pathway that is useful in tissue repair, but this stress-response is not useful in the culture dish, and the absence of the rest of the organism means that nothing will come from their growth decision, other than persisting under the damaging, stressful conditions.

In Hayflick's cell culture, the cells were clearly under sufficient stress to activate their estrogenic cell division process, but in the absence of either adequate energy or appropriate signals, they were on a dead-end path. The specific substances in the culture medium could be investigated if we needed to know the detailed cellular physiology of that dead-end path, but giving serious scientific consideration to Hayflick's doctrine is itself a dead-end path.

The editors of *Experimental Cell Research*, who devoted 36 pages to the 1961 article, and 22 pages to the 1965 article, bear a portion of responsibility for publishing ridiculous, illogical, unfounded, and simply false statements; it would be hard to identify any standard of quality that was followed in accepting those articles for publication. The mass media can't be blamed too much in this case, because the scientific media themselves have been manipulated.

To talk about "reversing aging" by adding telomerase to cells reminds me of the advertisements for an apparatus that allowed you to recline with your head lower than your feet, except that when you age upside down, by lying around on that device, there is a silly grain of truth in the claim that you have "reversed" the aging process.

The fact that cells are always open to "reprogramming," which simply means responding appropriately to their environment, is an important thing to keep in mind. Alexis Carrel's experiments are still the best demonstration that biological aging is essentially a response to something in the cells' environment. Carrel's emphasis on fats as an important aspect of aging is massively supported by research in nutrition, organ transplantation, and tissue culture.

It is now clear that estrogen is intimately related to the universal stress-reaction system, the heat shock proteins. Progesterone, the most direct and general antagonist to estrogen, is now seen to be involved in this fundamental system--it opposes the actions of the stress proteins, and the stress proteins mediate the factors which cause a progesterone deficiency.

Progesterone, thyroid, saturated fats, and light are primary antistress factors which have already been shown to protect against some of the effects of aging (such as autoimmune

Les H.S.P testo et estro shift la différenciation cell vers dédifférenciation

reactions), and against the stresses which contribute to aging, and in many cases to reverse age-associated changes that have already occurred (such as regenerating the thymus). To fully reverse aging we need to know all of the factors that cause it; Dolly is proof that adult cells are not, in themselves, "old," and is confirmation that Carrel was on the right track.

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whether a glial stress response is implicated in estrogen-induced granulation. **Our findings indicate that estrogen elicits a heat shock response and subsequent granulation in astrocytes residing in estradiol receptor-rich brain regions including the arcuate nucleus and the wall surrounding the third ventricle but not in estradiol receptor-deficient regions such as the striatum and corpus callosum. The heat shock proteins induced by estrogen, namely, the 27, 72, and 90 kDa stress proteins, are upregulated in astrocytes in response to oxidative challenge supporting our hypothesis that estrogen mediates senescent changes in the rodent hypothalamus through oxidative mechanisms."**

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Wu WX, Derks JB, Zhang Q, Nathanielsz PW, Endocrinology 1996 137(12):5685-5693 "Changes in heat shock protein-90 and -70 messenger ribonucleic acid in uterine tissues of the ewe in relation to parturition and regulation by estradiol and progesterone," "Steroid receptors, including estrogen receptor (ER) and progesterone receptors (PR), form associations with heat shock proteins (Hsps). **Dissociation of Hsps activates PR, whereas retention of Hsp90 in vitro stimulates ER**. Progesterone and estrogen, interacting with their receptors, regulate myometrial contractility throughout pregnancy and during parturition. We hypothesize that uterine ER and PR changes concurrent with changes in Hsp90 and -70 abundance could alter uterine function." "Dramatic tissue-specific increases in Hsp90 and -70 mRNA were observed in myometrium and endometrium ($P < 0.05$) during spontaneous and glucocorticoid-induced labor. Hsp90 and -70 mRNA localized in myometrial, arterial smooth muscle, and endometrial gland epithelial cells. Estradiol increased Hsp90 and -70 mRNA in myometrium and endometrium of nonpregnant ewes. Progesterone did not affect Hsp90 and -70 mRNA abundance, but **inhibited the estradiol-stimulated increase.** These data support our hypothesis that at term, increased abundance of Hsp90 and -70 may inhibit uterine PR and stimulate ER function in uterine tissues. Similar changes, if present, would be of importance in species showing no progesterone withdrawal before labor, such as primates, including pregnant women."

Zeman EM, Pearson CI, Brown JM, Radiat Res 1990; 122(1):72-76, "**Induction of hypoxia in glass versus Permanox petri dishes,**" "The survival of Chinese hamster ovary cells in culture following graded doses of X rays delivered under aerobic and hypoxic conditions, or treatment with the bioreductive drug SR 4233 under hypoxic conditions, was evaluated as a function of whether cells were plated onto glass or Permanox plastic petri dishes. In the case of treatment with SR 4233, the influence of varying the total volume of medium in the dishes was also studied. While the **Permanox petri dishes were sufficient to yield "radiobiological" hypoxia,** that is, oxygen enhancement ratios of approximately 3.0 were obtained for X irradiation, they were inferior to glass petri dishes with respect to the hypoxia-selective cytotoxicity of SR 4233. For a 90-min hypoxic exposure to 40 microM SR 4233, the surviving fraction of cells plated on plastic dishes averaged about 50-fold higher than that of cells plated on glass dishes. Although varying the total medium volume did affect the extent of SR 4233-induced cytotoxicity for glass dishes--drug toxicity decreased slightly with increasing medium volume--this was not the case for the plastic dishes, in which the cell survival following a fixed SR 4233 exposure was essentially constant as a function of medium volume. These results suggest, at least for SR 4233, and under these experimental conditions, that Permanox petri dishes are not satisfactory for such studies."

Ray Peat's Newsletter

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I wrote this several years ago, but each month there was always something more topical to send out. Every day, the mass media publicize and promote dangerously mistaken ideas, so there was always a more urgent seeming topic.

I always try to place concrete subjects in their most appropriate context. As a person who studied and worked in linguistics, literature, and art before concentrating on work in biology and physiology, I realize that language, imagery, and metaphor always work within a specific cultural setting. Seemingly infinite amounts of money can be mobilized by strong metaphors. The War on Cancer, the War on Drugs, the Genome Project, are examples of using language deviously to manipulate the public. Every issue, scientific or political, to be considered sanely, requires that we look critically at the contexts, and the contexts include the words, the concepts, and the metaphors that we use to communicate with.

Culture is the context for political power. **I have often discussed topics in biomedical research which reached their highest achievements in the first half of the 20th century, and then declined in the second half of the century, under the influence of the pharmaceutical industry, and its servant, the U.S. F.D.A., but this was only one aspect of a general process.**

A great and deliberate pollution has been spread through world culture. While the U.S. Government was secretly using Americans as guinea pigs for experiments with radiation and germ warfare, it was secretly spending vast amounts of money (most of it from the Marshall Plan) to support Abstract Expressionism in painting, and parallel movements in other arts and sciences. The CIA-funded Congress for Cultural Freedom was representative of the way this public money was used to eliminate freedom of expression. "Liberals" and "progressives" were special targets for this manipulation, but even conservatives such as Henry Luce (publisher of *Time* and *Life*) were induced to stop ridiculing Abstract Expressionism, and to begin supporting it.

The suppression of critical judgment in art makes it easier to suppress it in science, medicine, and politics.

I. Public Passivity and the Screw
II. Phenomenology of the State: Marxism according to Groucho
III. Education for the Primacy of Paranoia

I.

The sports hero, the "world class performer," the producers of grand spectacles, by definition are "excellent," better than everyone else at what they do. When the culture is filled with grand achievements, admiration is an appropriate reaction, and participation isn't. Almost the whole population falls between the Olympics and the Special Olympics, in all sorts of abilities, but their culture is created from the top down. Similarly, small businesses are squeezed out by monopolies, craftsmen are replaced by computer programs, insurance companies regulate the professions. And as excellence becomes a theoretical standard, everyone's performance is debased. The "quality" that people like Donald Trump admire is unlike the qualities that people used to enjoy.

"Freedom is not a concept in which people can do anything they want, be anything they can be. Freedom is about authority." ***Mayor Giuliani, New York Times, March 17, 1994***

Several years ago our local newspaper and television music critics raved about the "acoustics" of the city's new 22 million dollar concert hall. I had always wanted to hear Yehudi Menuhin play, so when he came to town I got a seat up near the ceiling, where I was startled to find that the sound was coming out of loudspeakers mounted in the ceiling. Electronically processed sound, generated by vibrating metal and plastic loudspeakers, can be heard even better at home, without the "acoustics" of the concert hall.

The "quality" is in the minds of those impressed by the cost of the building.

The words "client" and "patient" express the passivity of the customer in relation to the lawyer or physician. The same passivity exists wherever "expertise" replaces self-reliance. The individualism that was idealized in America has been replaced by a client mentality.

The authority of power can't be questioned if the people don't have their own knowledge, ability, and power.

II.

History attempts to make time coherent, logic tries to transcend the incoherence of history, and phenomenology tries to find meaning, purpose, and motive in the incoherence and illogicality of our social experience, primarily by eliminating false assumptions. Governments and their educational systems are in the business of preserving false assumptions.

The theory of monarchy is that only one person has to think, so the citizen-subject can be thoughtless. Other political philosophies are one-thoughted, two-thoughted, etc., depending on how little reality they admit. Hegel tried to get complexity organized into the simplifying monarchy of the thought of god. Marx took the idea of the dialectic, and used it to generalize reality, but underestimated the difficulty of clearly defining generalizations such as capital, when the boundaries of the system were in a continuous process of reformation.

When knowledge and culture become important parts of capital ("intellectual property," and judicially recognized "expertise" for example), the ambiguities demand that the contributions of Groucho Marx be considered as an extension of classical marxism. Groucho said he wouldn't want to belong to any club that would have him. To recognize the ambiguities of class and power is to begin to grasp the phenomena of society. Identity and belonging, language, concepts, names and origins seem more important than physical realities. And that fosters the growth of a culture of fraud and deception. Advertising, lobbying, and bribery blend smoothly with art, science, and law.

Any statement, no matter how clear and logical, depends on context--even scientific and mathematical statements. Goedl's principle and computer-program glitches illustrate the idea. Any statement demands a clarifying context, and therefore a dialog. That's the meaning of the "dialectic" introduced by Hegel and expanded by Marx. Everything has to be made clear by discussion. Reality is more complex than any attempt to formalize it. The reality is that laws and contracts function primarily as traps, to give the appearance of reason to acts of power. Contracts with insurance companies, publishers, and state agencies are famously meaningless, but *any* contract or law of importance is nothing but an opportunity for powerful groups to use the force of money and the courts (or police and their weapons) to defeat those who would assert some "right" under the law or contract.

"The most important Manhattan Projects of the future will be vast government-sponsored inquiries into . . . the problem of making people love their servitude."

"To make them love it is the task assigned, in present-day totalitarian states, to ministries of propaganda, newspaper editors and schoolteachers. But their methods are still crude and unscientific."

Aldous Huxley, 1946

People who consider themselves to be the state (whether or not they say "the State, it's Me") have almost an identity with the Law. Laws were written in the past, and since the past isn't accessible, it's almost as though a foreign power ruled us from a distant imperial capital, and sent its agents among us to apply the law to us as they see fit. They are agents of the state, interpreting the law for us, so that we may be bound to it. As soon as they perceive themselves to be agents of the state, their thought becomes the law.

The problem relates to social workers and lawyers as much as it does to presidents and attorneys-general--their subjectivity fills not only their world, but it intrudes into everyone else's

world. Lawyers and presidents lie, not just because they can get away with it, but because it has become part of the job description.

The basic question about the state is where its legitimacy comes from. The monarch used to speak for god, and his clergy backed him up. Republics kept the basic idea of the state, and invented a new story about its legitimacy. But the new government is always founded by traitors to the old government. Treason is the essence of the state. Treason is legitimacy.

The official implementation of the policy of Loyalty Oaths made it clear that the government of the United States aspired to totalitarian perfection. The same government had secret policies, secret laws, secret programs, and acknowledged that it had to lie to its citizens. Citizenship amounted to an arranged marriage between an eight year old virgin and a syphilitic pirate.

If everyone who is now in prison were released, and put into the jobs of government officials, filling them from the top down, and deciding among themselves who would go to congress, who to the executive branch, to the courts and state governments, nothing would get worse, and it might get better, because the question of legitimacy would be settled, and the cost of bribes and campaign expenses would be smaller.

Jury nullification is one of the few situations in our democracy in which democracy and reason can sometimes be seen in action, but it is limited by the way juries are constituted. People who are homeless can't serve on juries, and neither can people who need more to pay the rent than the $10 per day jurors commonly receive. Under Jim Crow laws, white people always tried black people. If juries really reflected the population in general, or if they were actually chosen from the peers of the accused (most prisoners are poorer than those who condemned them), fewer of those accused would be convicted.

Capital punishment, under our system, never punishes capital. If a corporation's officials deliberately take actions that they know will kill people, it has committed first degree or aggravated murder, and so its capital, all of its capital, should be taken from it, as well as from those who took the action. It is protested that "innocent investors would lose their money," but the protest makes evident the truth that corporations are designed to let people get away with murder for profit. If a corporation is to be anything but a conspiracy against the public, it must be fully responsible for its actions. Investors, to protect their money, would have to know what was going on in the corporation. This is exactly the principle that is now in practice regarding the confiscation of property involved in certain crimes, primarily drug crimes, but the reasoning would be even clearer if it were applied to the corporate property involved in corporate crimes.

The principle that no valid contract can be made to do something illegal takes legitimacy away from corporations--and governments--which are used to commit crimes, with simpler logic than that used in confiscating airplanes used to smuggle drugs. Likewise, a clause or implication of a contract which is secret from one of the parties to the contract is a logical impossibility, and makes the contract a nonentity.

If a corporation is a conspiracy against the public, with a prerogative to keep secrets for its own profit, any government which has any secrets from those it rules, is a conspiracy against them, for whatever reasons it might have. The right to have secret information is the right to lie, to rob, and to kill, and those who assent to such governmental power have no claim to legitimacy as citizens. Any governmental action which is kept secret constitutes evidence of the government's illegitimacy.

If power must be open to be legitimate, then the power to determine the intellectual content of any educational curriculum must be open. Governmental power is behind every recognized educational institution, but nearly all decisions about the accreditation of those programs are made in private. **If the reasons for imposing certain curricula were open to full discussion, then the educational programs would also be more likely to incorporate the principle of responsibility and evaluation.**

As funding for education shrinks, the state is seen to be exercising thought-control, in a simpler and more direct way, when it specifies the

curriculum that must be followed in home-schooling. When the state accredits educational programs, or establishes private accrediting agencies, it is delegating thought-control to the accredited, or accrediting, agencies.

If the state, through its accreditation system and its court system, can define what an expert is, then it can define what knowledge and truth are. The loyalty oath was the blunt object used by Adolph Hitler, Strom Thurmond, Richard Nixon, et al., to keep people in line. Education and its accreditation, backed up by a prison system, are the high-tech equivalent of the loyalty oath, controlling the intellectually limited public as effectively as the old system controlled the morally atrophied.

Approved knowledge is made tantamount to citizenship. Even beauticians have to be licensed by the state. Schooling is the moral equivalent of syphilis, but piracy is the prerogative of the corporate-bureaucratic elite.

As long as knowledge is power, and power is (able to define) knowledge, secrecy and ignorance will be promoted and knowledge will be rationed.

Schools are already in the business of rationing knowledge. The idea and practice of "challenging examinations," being able to get credit in a course if you already know what the course is supposed to teach, has essentially disappeared, because, as Oregon's Secretary of Public Instruction Gubser told me, "what students know doesn't have anything to do with education." In my dealings with other state, federal and private accreditation officials, I understood that to be their functional attitude, but when I heard the state's top official blurt it out after her evasions had failed to dissuade me, I realized that the system was consciously conspiring against knowledge. If people could get their diplomas just by proving their (conventionally recognized) knowledge, they would have too much time to spend learning about reality.

I have heard many teachers say that it is impossible to measure how much a student knows, and my question has to be, "then how can you know that?" And why are exams used to choose candidates for college admission, or to enter the practice of medicine or law, or to get a driver's license? Teachers, for whatever reason, function as part of the mystification that creates the knowledge rationing system. Alfred Jarry was describing schools and governments when he wrote about the "debraining machines."

The great danger now is that critical consciousness is becoming so rare, that the State will be able to extend the concept of "contempt of court" to the administratively punishable offense of "contempt for the legally constituted knowledge." The mechanisms already exist for doing this. Forty years ago, Wilhelm Reich was imprisoned, and his books were burned. *The Mass Psychology of Fascism,* which analyzed the dirty little character defects of authoritarian officials, was destroyed as a "label for a medical device." *The Murder of Christ, Listen Little Man, The Function of the Orgasm,* and other books about the nature of social oppression and violence were not even available to graduate students in psychology. The academic apparatus in its entirety conspired to maintain the official silence while Reich died in prison.

At least until it is illegal to do so, we should continue to ridicule, criticize, satirize, and condemn the state power which is in itself an abuse of reason and justice. Let there be a new world disorder!

The attitude toward the past is everything. The past, by definition, is unalterable, and can't be present again. Examining the record, we can see how we got where we are, but knowing where we are going is part of the life process itself. Blake said, "Imagination has nothing to do with Memory."

Those who try to "preserve the past," by trying to make it live again, in effect are trying to gain immortality by imposing death onto life.

Institutions are things that persist from the past, in someone's way of life and attitude, that are imposed onto life, over and over. Circumcision is a metaphor for every institution. The living flesh is trimmed, pain is inflicted, attitudes are repeated. "As the caterpiller chooses the fairest leaves to lay her eggs on, so the priest lays his curse on the fairest joys."

Logic that works for established knowledge can't work for projecting the future. Logic

clarifies and orders the past, but lived intelligence, imagination, is the mental tool that is appropriate for the future, which is the only place we can live.

We can get along very nicely without the debraining machines.

III.

If the schools and universities have the purpose of training people to be good employees, then only the first two years should be required, to teach reading and counting. At the age of 8 or 9, the practical career studies could begin, in engineering, medical services, judicial and military services, food preparation, and entertainment services.

But, if people were to be prepared to function as citizens, to make decisions about how their lives were to be lived, then the process of education would be based on criticism, evaluation, and on seeing things in all the relevant contexts that can be imagined. And the process of education and criticism would move toward the center of our lives, and would be continuous, from infancy to old age.

A wonderful variety of stupid beliefs has been propagated from the centers of academic power, and each type of stupid belief has tended to reign for a generation, until a new, more oppressive stupidity has been invented and imposed in its place. The impossible ideas can be propagated, because the educational system never learned how to teach people to recognize when the emperor's new clothes don't exist, and to say so.

When everyone is talking about the emperor's new clothes, the person who trusts his senses will perceive that a false belief is being propagated when he sees that the emperor is naked. To talk about the imposition of lies is to risk being classified as a "paranoiac." If everyone discussed the alternative interpretations that seem reasonable, then evidence would be evaluated in relation to theories and assumptions. **The basic violation of reason then would be the authoritarian refusal to discuss the issue.** Secrecy for national security would be recognized as the equivalent of a coup d'etat, taking authority away from the public. .

The culture of computation is a development of authoritarianism. Computers were conceived as mathematical machines, to work out the implications of premises. Mathematics was always popular with the established powers, because it never questioned assumptions. The computers that have been developed into manipulators of images also make the manipulation of people easier.

The "critical paranoia" that Salvador Dali described was the basic mental process that used to be called "wonder," guided by the critical evaluation of alternatives. The questioning curiosity aroused the speculative imagination, and the quality of the perception--the richness of the discovery--was suggestively related to its truth and significance.

To be concerned with the meaning of life and the quality of life is to wonder whether "this is all there is," and to live in a state of exploration. An educational system that is dedicated to the preservation of things as they are, must stifle that natural exploratory impulse. Because if it isn't stifled, that impulse will look for a better way of living. Our nature, so far, has been extremely antagonistic to our nurture, and from that opposition the system has created the ideas of original sin, corruption of the body, bad instincts, genetic determinism, neokantianism, professional training, and all of the other denials of essential human intelligence.

The nature of our biological development requires that the organism function and interact with the environment as it grows. Education of the intelligence is intrinsically related to the proper growth and function of the organism which is the person. The lack of stimulation or the wrong kind of stimulation makes us sick, ugly, and stupid. Schooling plays its part in degrading intelligence, but the whole culture is structured to warp our growth into forms that are convenient for the functioning of the system as it is.

The argument for realism and bottom-line practicality is often made, that accountants must be trained to help corporations grow, and that people would naturally prefer to learn something more pleasant than accounting, and so there must be extrinsic inducements and coercion. But the higher realism and practicality argues that human consciousness and existence must have priority

over any of the economic mechanisms that might support a particular way of living.

The priority of human intelligence specifies the means that are appropriate for education in any setting. Intelligence is, by definition, responsive, and responsive intelligence is necessarily responsible. The sources of power in a society are always integrated with the educational process, and the manipulative use of control has always made the process of education disappear.

The free use of education amounts to the attempt to solve the problems of society, and so education and intelligence would be of service to society. The universities in third-world countries have always been recognizable as servants of the ruling classes or imperialists, but Europe and the United States have fostered a perception that universities existed to serve the public and to educate for democracy.

If there were no secrets, power would be administered in the open, and there would be no conspiracies, or rather, the ubiquity of the process would be evident, and a different term would be used. But general awareness of the exercise of power--stupid as power's actions have always tended to be--would make things hard for those in power. And so any factor that fosters a suspicious, critical, imaginative, exploratory awareness and questioning of the world tends to weaken the concentration of power, and to share in the exercise of power. Intelligence, as far as it exists, tends to be revolutionary, and so education (if it is essentially an exercise and development of intelligence) must be devoted to the overcoming of stupidity, especially when stupidity rules.

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Frances Stonor Saunders, ***Who Paid the Piper: The CIA and the Cultural Cold War*** (London: Granta Books), 1999; ***The Cultural Cold War: The CIA and the World of Arts and Letters.*** New York: New Press, 2000.

Pages 397-404: Tom Braden, director of the International Organizations Branch of the CIA, said that by 1953, "we were operating or influencing international organizations in every field" (page 398). When the source of their funding was revealed many of the people claimed not to have known, but Braden shows that they had to have known.

A. C. Higgins, State University of N.Y., Albany, commenting on ***Creating the Cold War University: The Transformation of Stanford,*** Rebecca S. Lowen, Berkeley, California: The University of California Press, 1997:

"There's not a word in this book about fraud and dishonesty in science. What is abundantly clear however is the transition from the 20th century university to the "Cold War University," a transition which is necessarily accompanied by the loss of idealism and the core values of science. This new science is a prostitute variety, ready for any comer on the open market. What is important to the academic administrator of the Cold War University is the bottom line. Why should anyone expect honesty in such an institution? Indeed, it's no wonder that fraud and dishonesty are as common as they are. What is amazing is that honesty and morality remains at all! It's now been 40 and more years since "entrepreneurial science" was substituted for the older stuff. After 4 decades, is anything of pure science left? Should we be surprised at anything that happens?"

Ivan Illich, from the introduction to ***Tools for Conviviality,*** 1973:

"Our analysis of schooling has led us to recognize the mass production of education as a paradigm for other industrial enterprises, each producing a service commodity, each organized as a public utility, and each defining its output as a basic necessity. At first our attention was drawn to the compulsory insurance of professional health care, and to systems of public transport, which tend to become compulsory once traffic rolls above a certain speed. We found that the industrialization of any service agency leads to destructive side effects analogous to the unwanted secondary results well known from the overproduction of goods. We had to face a set of limits to growth in the service sector of any society as inescapable as the limits inherent in the industrial production of artifacts. We concluded that a set of limits to industrial growth is well formulated only if these limits apply both to goods and to services which are produced in an industrial mode. So we set out to clarify these limits."

"The only source of knowledge is experience."
Albert Einstein

Ray Peat's Newsletter

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Bioelectric Fields, Regeneration, and the Lactic Acid Myth

Exercise physiologists, knowing that lactic acid is produced during intense exercise, and cancer biologists (especially since Warburg's work showing that all cancers have a respiratory defect) who know that cancer tends to produce lactic acid, almost always talk about the "acidity" of the fatigued muscle or of the cancer cell.

While it is true that the entry of lactic acid into the blood tends to produce metabolic acidosis, the cell which is producing the lactic acid is actually more alkaline than normal cells. The simplest way to think of it is that "acid leaving the muscle makes it less acidic." But still, even though the chemical formula for producing lactic acid directly shows the consumption of acidity, and direct measurements confirm that the cells become more alkaline when they produce lactate, the average biochemist or physiologist is likely to think the opposite.

What we call inflammation offers a good conceptual link between the studies on excitotoxicity or cellular stress, and the newer approaches to the treatment of aging and degenerative diseases, based on ideas of regeneration and development. Controlling inflammation becomes part of promoting regeneration. Injury potential and inflammation are closely related; for example, I found that sunburned skin, or skin irritated by the application of a prostaglandin, had a negative polarity relative to normal adjacent skin.

Lactic acid (or its ion, lactate) is involved in stress, aging, edema, inflammation, rheumatic diseases, bioelectricity, nerve-muscle interactions, cancer, and the antiinflammatory actions of the thyroid hormone, among other things, so a fundamental confusion about what it does to cells means that much of biological and medical opinion has been unfounded. When I discussed the cellular alkalinizing effect of lactic acid formation in my dissertation in 1972, it wasn't a matter of scientific dispute, and since then, the newer techniques of measurement have made the situation even clearer. But, even today, almost always when conclusions are drawn about muscle fatigue, cancer, radiation damage, etc., they are based to a large extent on the false assumption about lactic acid and cellular pH. A specialist too often builds on the generalizations that are propagated by textbooks and other mass media.

When the pH of a cell or tissue changes, its electrical properties change.

In the normal body, repair is going on constantly, and generally the new substance conforms to the existing pattern. The systems of signals that govern these patterns are called 'developmental fields,' and during the last 80 years, evidence has accumulated showing that electrical fields participate in these processes of organization. (Child, 1921; McCaig, 1996.)

There is an electrical field around organisms and, internally, electrical fields contribute to the development and maintenance of anatomical structure. Sharks are able to find small fish buried under sand by detecting their electrical fields; they will dig for electrical devices that have similar fields. Large electrical fields have been demonstrated extending away from the surface of skin, and since these fields have some of the properties of a "static electrical field," many people have assumed that the charge was just something that passively accumulated by friction.

Le champ ext alligne les molecule de la substance et ce donne une charge Polarize

But an experimenter demonstrated the presence of an electrical field extending outward from the external surface of pieces of skin grown in a culture dish. When cyanide was added to the medium, blocking respiration, the field collapsed, and when the cyanide was washed out of the skin, allowing respiration to continue, the field reappeared. The intensity of respiration clearly governs the intensity of the field. The researcher suggested that the field had the characteristics of an "electret" field. An electret is a charge polarization that results when the molecules of a substance (wax or ceramic) are aligned by an external field while at a relatively high temperature, and then cooled.

He implied that the energy of respiration was causing an alignment of molecules, resulting in the polarization of charges. Any field of this sort will influence other charged particles, and so it is obvious that it will participate in the arrangement and organization of particles. The existence of such fields probably influences the alignments of particles within cells, and of cells within organs. There is a tremendous difference in the strength of the field produced by different individuals, but the pattern is always essentially the same, except when it is distorted by pathological conditions; tumors, for example, distort the field.

In general, cell excitation or stimulation increases the intensity of cellular respiration, but when oxygen isn't available, the stressed or dying cell may become hyperactive. Epileptic seizures, for example, can be produced by hypoxia or hypoglycemia, as well as by other stimuli such as imbalances of salts and water.

Textbooks often represent cellular electricity with a diagram showing the outside of a cell as "positive" relative to the "negative" inside of the cell. And researchers who have read those textbooks uncritically sometimes speak of the "positive" charge or field outside a cell. I'm sure they won't feel humiliated if I point out that the whole thing is an artifact of their experimental setup. Isolated cells in a liquid will move toward the positive pole in an electrical field, showing that the cell outwardly has a negative charge. This is called the sigma potential, or surface potential. And if the cell is pulverized, again, nearly all of its large molecular componenents and organelles will move toward the positive pole.

When an electrode is poked into a cell, it registers a negative polarity relative to the neutral outside. On a larger scale, if you put one electrode on moist skin, and put another electrode on a cut, the cut skin will be negative relative to the intact skin. This is called an "injury potential." But the intact skin is itself negatively charged, in the same way that any whole cell is negatively charged.

It has been suggested that sharks are attracted to wounded animals by the electrical field caused by the injury, rather than by the odor of the blood, since they can detect the injured animal from distances far beyond the spread of chemical substances from the blood. The animal's "injury potential" is apparently just an intensification of the animal's normal electrical field. (Although much of the research on electrical sensing has been done on fish, I suspect that land animals sometimes use electrical sensing. For example, dogs can sense an impending epileptic seizure of their owner; the electrical fields created--by the brain or the skin--during an extreme metabolic disturbance might be larger than those of a small fish buried under sand. People are able to detect the flow of a weak current in a buried wire, as discussed by Barnothy and Barnothy in *Biomagnetics.)*

I have seen articles in major science journals that draw important conclusions from the nonexistent positive charge supposed to be on the outside of cells, and those things have got past the editors and referees because those ideas are so current in our scientific culture. Less blatant, but equally false, ideas are even more prevalent. The use of various microelectrode techniques has produced an abundance of information on cellular electrical responses, but with the exception of the work of Gilbert Ling and a few others, the meaning of the data is obscured by a huge culture of phantasy theories.

With this sort of fundamental confusion about bioelectricity, it isn't surprising that there is so little interest in the morphogenetic influences of

Intensité de la respiration cause un alignement des molecules et qui resulte en polarization des charges

excitation ou stimulation ↑ l'inten de la Respi, mais si O_2 n'est pas disponible les cellule mourant ou stressé peuvent devenir Hyperactive

electrical fields. The textbook images of "membrane potential" give the impression either that relevant fields don't exist, or that they are the opposite of those observed experimentally, and those mistaken textbook images overwhelmingly dominate the scientific-political-economic scene.

The overall charge on proteins and other macrolecules is, in general, a matter of the pH of their environment. Usually, cellular proteins have a negative charge above a pH of 5. The ionization of chemical groups such as hydroxyl, amino, and sulfhydryl are responsible for the overall charge. The degree of oxidation or reduction affects the number of sulfhydryl groups, and the structural state of the protein also influences the charge. At high pH the charge is high, and the number and arrangement of sulfhydryl groups can affect the charge. The presence of small ions, carbon dioxide, and oxygen also influence the charge of proteins. When the whole living system is involved, bioelectricity interacts with other electron-related phenomena, including oxidation-reduction, pH, donor-acceptor and free radical reactions.

When the pH of blood is high, the cells of blood vessels are excited into contraction. When the pH of the blood is low, nerve activity can be dulled to the point of coma, as in diabetic acidosis. I think these effects of pH, and the simpler effects of pH on protein charge, are closely related to each other, and to the phenomenon of the injury potential.

Since proteins are generally negatively charged, and tend to move toward the positive pole when they are in an electrical field, a membrane made up of proteins (sheets or layers of cells, for example) will move in the same direction relative to the water that permeates it, meaning that the water will move in the opposite direction, i.e., toward the negative pole. This is called electroosmosis. Since the electrical charge on proteins becomes more strongly negative when the pH is high, and less strongly negative when the pH is low, water will tend to move across membranes from acidic regions into alkaline regions.

The contracting muscle tends to take up water, and forcing it to take up water increases its tendency to contract.

Oxygen, producing carbon dioxide, acidifies the cell, and carbon dioxide influences the cell's handling of water. Carbonic anhydrase inhibitors are commonly used to regulate conditions involving edema, including adaptation to high altitudes.

During intense contraction, especially when oxygen and carbon dioxide are limited, muscles produce lactic acid, and **the specific reaction in which lactic acid is formed causes protons to be consumed, that is, it raises the pH.**

Increased pH, decreased osmolarity, and the associated movements of ions increase the cell's excitability.

Because of the long history of thinking of muscle fatigue and hypoxia in terms of lactic acid production, and the mistaken idea that intracellular pH is more acidic in proportion to the production of lactic acid, the confusion of biolectrical ideas has been compounded by the confusion about pH.

Cellular excitation, exhaustion, and injury will affect the cell's electrical fields in different ways depending on the availability of oxygen, glucose, salts, etc., but **in each of those states, there is increased entry of calcium into the cytoplasm.**

Calcium's entry into cells in itself can lead to increased excitation (muscle contraction, cramps, and seizures, for example), to cell death, or to increased proliferation. (It has also been thought that sodium and water can stimulated proliferation. For example, Berman, et al., 1995.)

Something as simple as reducing the pH can prevent apoptotic ("organized" or "programmed") cell death. (K.P. Hanson and V. E. Komar, *Molecular Mechanisms of the Radiation Death of Cells,* Energoatomizdat, Moscow, 1985).

Carbon dioxide, produced by respiration, and ATP hydrolysis, are two powerful acidifiers of the cell; with sufficient stimulation both can probably act simultaneously, and in this situation the pH decrease will tend to oppose the exciting stimulus. Without sufficient oxygen to make CO2, a given stimulus might cause greater excitation and probability of death. The insufficiency

of oxygen also leads to a relatively reduced state of the cytoplasmic proteins, increasing their electrical charge at a given pH. **CO2 has many other effects that act in the same protective direction, such as calcium removal, iron binding, and water binding,** and these other effects are at least as important as the pH effect. (Badylak and Babbs, 1986 showed that the combination of a calcium blocker and an iron chelator with carbon dioxide tripled the survival after 7 minutes of cardiac arrest.) Adequate CO2 is intimately involved in the disposition of calcium, and calcium's regulatory significance is universally recognized.

K. P. Buteiko believed that increased carbon dioxide in the body fluids sometimes caused cancers to disappear. In many studies over the last 40 years (and the trend can also be seen in insurance statistics published in 1912), it is clear that cancer mortality is much lower at high altitude. Under all conditions studied, the characteristic lactic acid metabolism of stress and cancer is suppressed at high altitude, as respiration is made more efficient. The Haldane effect shows that carbon dioxide retention is increased at high altitude.

Studying athletes at sea level and at high altitude, it was seen that less lactic acid is produced by maximal exercise at high altitude than at sea level. Since oxygen deficiency in itself tends to cause the formation of lactic acid, this has been called the "lactate paradox"; the expectation was that more lactic acid would be formed, yet less was produced. Something was turning off the production of lactic acid. Normally, it is oxidative respiration that turns off glycolysis and lactic acid production, so that in exercise beyond the ability of the body to deliver oxygen, and in cancer with its respiratory defect, glycolysis produces lactic acid. So, something is happening at high altitude which turns off glycolysis.

The Haldane effect is a term for the fact that hemoglobin gives up oxygen in the presence of carbon dioxide, and **releases carbon dioxide in the presence of oxygen.** It is the increased retention of carbon dioxide that accounts for the "lactate paradox." Carbon dioxide activates the Krebs cycle, but it also combines with ammonium, and in doing so, deactivates glycolysis because ammonium activates a regulatory enzyme. At high elevation, carbon dioxide is retained, and lactic acid formation is suppressed. (This is called the Pasteur effect, but altitude physiologists haven't begun thinking in these directions.) Comparing very low altitude (Jordan valley, over 1000 feet below sea level) with moderate altitude (620 meters above sea level), ACTH was increased in runners after a race only at the low altitude, **indicating that the stress reaction was prevented by a moderate increase of altitude.** (el-Migdadi, et al., 1996.)

The perspective we get on cancer, from the high altitude studies, allows us to go beyond the specific issue of cancer, to the more general issue of stress and regeneration. In outline, stress alters the physical nature of the cellular substance in a way that activates the cell, in which case it will either die from exhaustion, or grow into new cells. The replacement of injured cells means that mutations need not accumulate, and this renewal with elimination of mutant cells has been observed in sun-damaged skin. Among the many layers of form-generating and form-sustaining systems, the balance of electrical fields has a basic place.

Several investigators have demonstrated that internal cancers altered the external electrical polarity of the animal, increasing the negative polarity in a region near the tumor. In the late 1960s, I suspected that irritation or inflammation created an injury potential, similar to the "demarcation potential" of a cut nerve or muscle. I covered one arm so that a small spot would sunburn without exposing the surrounding skin, and in other spots I applied small amounts of prostaglandins, the "hormones" derived from unsaturated fatty acids. The sunburned area was distinctly negative relative to adjacent areas, and some of the prostaglandins (PGF, for example) produced a slight increase of negative charge. I think these changes reflect both intensified metabolism and increased pH caused by interfering with efficient cell metabolism. Lactic acid

production raises the pH, and high pH increases the ionization of most proteins.

The localized distortion of the electrical fields will participate in adjustments that should tend to restore the normal fields, with different processes occurring depending on how long the distortion continues. Ordinarily, the fields change in concerted ways during the rhythmic events of eating, excreting, breathing, and sleeping.

When a state of excitement persists long enough for the cell to produce an excess of lactic acid, causing it to become more strongly charged electrically, nearby blood vessels and nerves will tend to grow into the area, restoring normal energy supply and integrated functioning. (Lactic acid can be demonstrated to stimulate vascular growth by putting it near the eye's cornea, causing blood vessels to invade previously clear areas. In cell culture, McCaig demonstrated that nerve cells grow toward the negative electrode.)

When a cell has been damaged (as by radiation or toxins), its inefficiency creates a small *localized distortion* in the fields, which will stimulate processes of repair or removal and replacement, as far as the organism's resources allow. When a stress is great enough that the *entire organism* is exposed to lactic acid, the organism's adaptive resources are being challenged, and potentially harmful responses are evoked. For example, a sluggish liver can allow the blood lactate concentration to rise during stress, and this can lead to secretion of endorphins and pituitary hormones (Elias, et al., 1997). The endorphins can increase histamine release, and growth hormone increases free fatty acids; increased permeability of blood vessels can allow proteins and fats to leave the blood stream with cumulatively harmful effects.

In general, the factors that protect against harmful local activation of cells are also protective against maladaptive general responses.

The doctrines that explain aging, cancer, and other diseases in terms of the "wearing out of cells" have been based on the denial of the role of organismic patterns and fields in the regulation of events on the cellular and molecular levels. Those theories or doctrines have been popular because they fit the "reductionist" idea of science, which tries to explain the organism as a whole in terms of its smallest parts. The investigation of regeneration, which requires thinking in terms of patterns and fields, has been retarded by that essentially antibiological culture of reductionism.

Sodium and carbon dioxide are essential for maintaining the normal fields, and these substances interact in ways that cause both of them to be lost during stress. In hypothyroidism, sodium is persistently lost, as carbon dioxide is chronically replaced by lactic acid.

Both sodium (Veech, et al.; Garrahan and Glynn) and carbon dioxide--by stimulating the Krebs cycle, and keeping the respiratory enzymes active--help to maintain the normal level of ATP, protecting against stress and shock.

The interlocking fundamental features of cell excitation/relaxation, electrical potential, lactic acid/carbon dioxide, water retention/water loss, salt regulation, pH and energy level, allow us to visualize in a coherent way the biological meaning of stress and adaptation. Interacting with those physical-chemical events, there are many layers of biochemical and physiological processes that reinforce or modify them, including regulatory systems such as hormones and other biological signaling substances, nutritional adequacy, and the type of fuel used. The safest and most effective interventions will be those which support our basic organizational fields (sodium, carbon dioxide, balanced proteins, fruits, thyroid, pregnenolone, for example), and don't introduce distortions, as some drugs, foods, hormones, and supplements do.

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compared with liver the Na+ content was 2-fold higher, K+ was 20% lower, total Ca2+ was 8-fold higher (7.4 mumol/g wet wt) and total Pi 2-fold higher (8.5 mumol/g wet wt), suggesting the presence of insoluble calcium phosphate, **HCO3- was lower, total Mg2+ was similar in both tissues, but free [Mg2+] (calculated by two different methods) was approximately 5-fold lower in the hepatoma, as was [ATP]/[ADP][P(i)]. Because of an inadequate blood supply, tumors are often hypoxic with impaired Krebs cycle activity, low [ATP]/[ADP][P(i)] and rely mainly on glycolysis for energy. The rapid production and subsequent export of anionic lactate-from the tumor cell would be accompanied by H+.** This would account for reversal of the proton gradient and activation of the Na+/H+ exchange. The elevated [Na+]i would decrease the Na+/Ca2+ exchange, which would in turn tend to cause the accumulation of Ca2+ (and P(i)). Such calcification is a very common feature of tumor pathology. The data indicate the change in gradient of one ion (H+) involves alterations in the linked equilibria of many ions and also of energy metabolites and offers new insights into properties of tumors important both diagnostically and therapeutically.

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Notes:

[The living cell is different from most other electrically polarized materials in being able to adjust its charge, its affinity for small molecules and ions, and its shape. During stimulation (and contraction of a muscle), the phase potential may momentarily disappear as proteins' affinity for potassium, sodium, and calcium change, but the sigma potential doesn't, and may even increase slightly. The nature of the excited state is different in different environments, for example, at high altitude or in the presence of increased carbon dioxide, muscles don't contract as fully, and don't produce as much lactic acid during their maximal activity, as they do under conditions of high oxygen and low carbon dioxide pressure.]

[Increased carbon dioxide lowers the so-called membrane potential (Ling and Gerard, 1949), which I interpret as being almost equivalent to a lowering of the "injury potential." There are several more direct indications that carbon dioxide protects against destructive excitation. Muscle contraction is limited by increased carbon dioxide, and at high altitude, maximum exertion is limited, very probably because of the Haldane effect, in which carbon dioxide is retained in proportion to the oxygen deficit.

Carbon dioxide increases the association of water with proteins, a process analogous to lowering the temperature; both cold and high CO2 concentrations have a similar effect on muscle relaxation after contraction. (Howell, 1920)

A deficiency of carbon dioxide (as in hyperventilation) tends to cause epileptic seizures and muscle cramps, and is a factor in asthma and several other diseases (Buteiko) which seem to involve excessive cellular excitation. I think it acts by way of reducing the overall electrical charge of proteins, probably acting as a "cardinal adsorbant," in Gilbert Ling's sense--a molecule which, when bound to a protein, changes the protein's affinity for other molecules.]

[When a needle is poked into a cell, it obviously injures the cell, but the doctrine of the "plasma membrane" leads people to deny that what they are measuring is a type of "injury potential." They want to say that they are measuring a disequilibrium between the inside of the cell and the outside. (A disequilibrium has to be maintained by some charging mechanism such as a "pump.") They talk about the significance of the "membrane potential" as if the presence of the electrode hardly had an effect on the cell. And the surface (or sigma) potential always seems to be forgotten by these people, who think of the outside of the cell as "positive."]

Ray Peat's Newsletter

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Tissue Firmness and Elasticity, and Rothen's Resonance: Forgotten Physics and Aging

The most interesting problems exist exactly where the professionals assert that there is no problem at all.

The space between cells is of interest to many specialists, but it is relegated to the background in mainline medical thinking. In reality, the stuff between cells is the biggest part of a complex organism, and it contains many of the answers to questions of individuality, immunity, growth, aging, healing, sickness, and regeneration.

Respiration is essential for the existence of higher organisms, making it possible to maintain complex and adaptive structures, containing appropriately differentiated cells. I want to introduce some ideas about how respiration is involved in the creation of structures both inside cells and in the spaces between cells.

The idea of "containment in the cell" has directed attention away from the ways in which a cell knows what it is and where it is, and where it should be, what it should do.

The material in between cells has been dismissed as little more than glue, but it is where some of our most important things happen.

But first, I want to outline some of the mental habits and fixations that have been retarding biology and medicine for a long time, keeping people from thinking about these organismic issues.

THE BIAS AGAINST SENSITIVITY

In dead vegetable matter, "cells" were the empty spaces in the fibrous framework. Plants could be grafted or propagated from cuttings, making it clear that one type of plant tissue could generate the other types. The "essence" of plants was considered to be little more than growth, and their seeds had the disadvantage of introducing individual variation. Grafting and cloning animals didn't seem to work, and the idea grew up that the animal's essence was contained in the germ cell, while the plant's essence was in its vegetation.

"Contained" in the "cell," our "essence" had only to reveal itself. A man's semen was his essence, which introduced the soul into the egg, animating it. Replacing "preformationism" with "epigenesis" simply introduced the idea of individualism, by saying that a new individual came into existence by fertilization, but it didn't

Carbonated water is such a common thing, chemists are embarrassed to talk about it.

All the water in respiring organisms contains a considerable amount of carbon dioxide.

Carbon dioxide binds to proteins and to other amine-containing polymers, and dissolves in water, reducing the pH, so that the interactions of polymers and water are strongly affected by the concentration of CO2.

Carbon dioxide modifies biological materials and structures in and around our cells.

end the belief that our identity was "contained" "genetically" *within the cell.*

The neat little compartments seen in plant tissues became a sort of mental armature that no one questioned. Almost all of biology has been reduced to the idea that "the necessary information is *contained within* the cell, in its genes." The "Central Dogma" of molecular biology was stated as "information flows from DNA to RNA and from RNA to protein, and not the other way." To speak of cellular sensitivity (as Lamarck did) is to assert that information flows *into* cells; the fanatical opposition to Lamarck that has characterized biology in the 20th century has blended into a general hatred of "vitalism," the idea that life could be explained in terms of its special, living qualities. **The dogmatists insist that life must be explained in terms of physics as they understand it, and it happens that their "physics" is nothing but a doctrinal relic kept in place to justify their conceptions of biology.**

The idea that cells are governed by their responses to whatever surrounds them has taken a long time to develop, and the dogmatists still feel that there is something impermissibly "vitalistic" in the idea that cells are sensitive or responsive. To be sensitive is to receive information from "outside," and so the anti-Lamarckian ideas of evolution and adaptation were extended into the fields of development, immunity, aging, even learning. "Clonal selection" has been proposed to explain everything that happens in the organism, from development to cancer, because this view is compatible with the doctrine that information flows only from the genes to the cell; the cells simply die if they don't contain the necessary information. "Programmed cell death," in which a genetic code--a program, like a computer program--specifies the time at which a cell will die, is a characteristic part of this doctrine about the nature of a complex organism.

I think it is necessary to look at these established ideas, which are absurd and unfounded, because we are forced to wallow in them every day, until people have come to treat them as if they were intelligent, intellectually responsible, descriptions of reality; if we realize that silly ideas and connotations have been built into our language, then we can begin to give serious attention to the "anomalies" of science.

"Anomalies" are facts that don't obey the law, and so they are of special importance for anyone who cares about understanding things. If you have some parts left over after you have assembled a puzzle, maybe the puzzle wasn't correctly assembled. So-called anomalies are often the most productive places to look for solutions.

CELLULAR JUDGMENTS

That cells may be small or large or giant hasn't seemed problematic to most biologists. The assumption seems to have been that they "are big enough to contain their essential genes."

Once or twice, I have got biologists to talk about the question of how a cell knows that it is big enough to divide. I think the essence of their answer is something like "they count the molecules," which is to embarrassingly compound the puzzle, like the farmer who explained his marvelous ability to rapidly count the cows in a field by saying that he "simply counted the teats and divided by four."

The same kind of question can be applied to the thickness of layers of extracellular material, such as the basal lamina of capillaries. For example, granted that a cell should rest on a structure of a certain uniform thickness, how does a cell know when to stop secreting the material? When it is modifying the chemical composition of its extracellular matrix, how does it determine that the right composition has been achieved, when the substance is outside the cell?

Cells have to, in some sense, perceive themselves and their environment, because their environment is an essential part of their existence, governing what they are and what they can become. To understand the nature of cellular perception, we have to look beyond existing descriptions of what cells are.

In plants, the fibrous, cellulose-based walls between cells don't prevent all interactions between cells, but they do keep the cells from wandering, and they act as stable regulators of the cells' functions. Animal cells also have a carbohydrate-rich layer surrounding them, which

powerfully regulates their functions, but this layer is much more adjustable than the cellulose framework of plants.

The chemical and structural plasticity of this intercellular material is an essential part of the greater sensitivity and complexity of animals, and while it is now conventional to describe this material as part of a signalling and regulatory system, I think it might also be appropriate to think of it as **part of the cell's sensory system.** It forms a buffer zone around a cell that is strongly conditioned by the cell's own activity, and when this zone is altered by the presence of another cell, or when its composition changes because of injury or infection, the influence from that buffer zone has to change processes in the cell. **For example, if we compare these layers to a film of soap around a drop of oil, the surface tension--and therefore the shape--can change radically under the influence of physical and chemical agents, such as temperature, salts or acids.**

The forces inside cells that contribute to their shape, interact with external forces and with internal and external chemical reactions. The composition of the extracellular matrix is now known to have a profound regulatory influence on the cell's genes. The cell's "phenotype" (our phenotype is what we appear to be) is regulated by the extracellular matrix, in combination with a variety of hormonal, nutritional, and metabolic factors.

A DIFFERENT PHYSICS

In the study of cohesion, adsorption, radiation, diffraction, and resonance, there has been a strong tendency to avoid questions of the "ensemble," in favor of the unique, or at most double, event or situation--one or two atoms or molecules, one or two frequencies--and beyond that, to describe things with "statistical, stochastic, colligative" assumptions and methods. Crystallography is an attempt to understand ensembles of atoms or molecules, but it represents the opposite extreme of abstraction, letting geometry replace concrete data about events in time and place. What has always been left out is the way in which long range order interacts with local, and delocalized, energy. There have been observations with relevance to these issues, but they have been "left out" because they were "anomalous."

These interactions of the parts of an ensemble over distances many times greater than the size of an atom are of special importance for biology; they are where we find all the most interesting questions in biology.

The way the various "anomalies" fit together is a matter for a general revision of science, but in biology, **the work of Alexander Rothen gives us a tool for beginning to make sense of some of the realities of biology that have seldom been thought about.**

When I began studying biology at the University of Oregon, the bulletin board near the electron microscope room displayed some photographs of crystals that professor Bajer had been making. One of them showed a quartz crystal, over which a thin film of plastic had been coated. On top of the plastic film sodium atoms had been deposited, showing that they were being aligned in a pattern conforming to that of the underlying quartz crystal. The film was much thicker than the units of silicon dioxide in the underlying crystal, so the arrangement of the sodium atoms was obviously not being determined by either the position of the plastic polymer molecules, or the relatively remote individual silicon and oxygen atoms below the film, but somehow by a projection of the pattern of the quartz crystal. Order had been projected through the disordered layer of polymer.

Earlier, I had read some of Michael Polanyi's work with long-range effects in crystals, and knew about his adsorption work, in which the adsorptive force of the underlying charcoal was able to make itself felt through several layers of atoms, continuing to cause more atoms to condense from the gas phase. Later, multilayer adsorption was explained as the result of electronic resonance.

Rothen, using the techniques he had invented for measuring the thickness of extremely thin films, found that metal-plated glass slides, coated with albumin, would bind multiple layers of antibodies which were specific for the albumin. Or, before the slide was exposed to antibodies, it could be coated with a plastic (Formvar) film 120 Angstrom units thick, and still, **layers of**

antibodies up to 80 Angstroms thick could be adsorbed.

Polanyi's multilayer adsorption was considered impossible by the leading physicists of the time, but the simple idea of electronic resonance eventually made it possible for them to accept the facts. But Rothen's adsorption of multilayers of immunologically specific proteins was just too much.

A couple of years after I had seen Bajer's micrographs, I asked him about them, and he said he didn't remember; **already, the opinion makers in science had reacted to experiments in which cells appeared to be "feeling" an artificially constructed gradient through a plastic film, by claiming that photographs had revealed tiny holes in the films, and the cells had been reaching through the holes and feeling the gradient directly. The cheating cells (like mind-readers who peek through their blindfolds) had been "exposed," and all the long-range transmembrane phenomena had fallen into disrepute.**

Even if the cells were "cheating" by reaching through holes in the film, the fact that they could sense the direction of the gradient, and move consistently "up the gradient," was never challenged, and it wasn't explained how reaching through the plastic could allow them to evaluate the gradient on the basis of a few samples--that in itself might require a more complicated explanation than the original idea, sensing the gradient through a film, required. The meaning of this episode is that the most influential scientists will seize even an irrelevant criticism as an excuse for ridiculing ideas that violate their dogma.

But pores in plastic films, that cells might poke their fingers through, had no conceivable relevance to Rothen's work (nor to Bajer's). **Rothen's technique could measure the thickness of the layers of antibodies, and show that they were continuous layers, several antibodies thick.** Antibodies to albumin aren't supposed to bind to themselves. The technique was so simple that a physicist visited Rothen's lab, learned his technique, and then claimed to have invented it as a method for simplifying immunological testing. **But he wanted only the commercial value of Rothen's discovery, and ignored its essential importance.**

Rothen's specific long-range adsorption, like Polanyi's earlier work, simply couldn't be responded to in a rational way. A rational response might have been to reason this way: If the organization of the underlying material projects itself strongly into the environment, then patterns in the environment must also make themselves felt in the underlying material. The same mechanism would amount to an action and a perception.

There were fields such as metallurgy, in which long-range forces, and the effects of surfaces on crystal structure, were "normal science," but in biology, physics had been reduced to the ideas that were dominant in 1915.

The conformation of a large molecule is part of its biological or immunological specificity. The specificity of conformation of any molecule must participate in the specific nature of the ensemble, and that of the ensemble, in the individual molecule. For example, certain enzyme molecules are known to arrange themselves one way in the cytoplasm, and another, random way when they are examined in the unnatural environment of biochemist's test-tube.

Since Polanyi's multilayer adsorption was explained as a resonance phenomenon, the same term could be applied to Rothen's specific adsorption, without implying that we understand exactly how it works.

Rothen also showed that enzymes can act across the films. To me, the main importance of this would be to highlight the extent to which an archaic physical view has governed biochemical thinking. The action of an enzyme at a distance means that its catalytic region might be larger than previously supposed, but it also suggests that we can't generalize from the behavior of an enzyme dissolved in water, to its behavior in the cell, where it would be subject to the reciprocal effects of many other components of the complex system. Biochemists have claimed that "biochemistry couldn't exist if you doubted that the function of enzymes in solution is identical to the function of enzymes in the cell," but other

biochemists have demonstrated that **some of the most basic assumptions of biochemistry were mistaken (Bernhard, 1988), including the assumption that the enzymes of glycolysis act on substrates that are floating around in solution.**

Digestive enzymes, added to a solution containing the food materials normally digested in the intestine by those enzymes, failed to alter the food materials at a rate that could be compared to that of normal digestion. But when a formalehyde-fixed piece of intestine was added to the mixture, the reactions occurred at approximately the rate that is normal for digestion. Although in young infants digestion does happen in the fluid contents of the intestine, after the age of one, most of the action of the digestive enzymes occurs at or near the surface of the intestine, under the influence of the adsorbed enzymes. This is another clear example of the idea that enzymes are dependent on their environment.

Whether or not cells are able to "feel" what is beneath a plastic film, recent evidence indicates that the thickness and composition of the material they sit on does make a difference. Their genes are turned on by the structures that are sensed in the extracellular matrix, and the longevity, growth, function and death of the cells are determined by the nature of the substances outside the cell.

The implication of much current research is that if all of the specific protein filaments can be identified that form links between the structural filaments inside cells and the matrix materials outside the cells, the powerful influence of the external matrix on the cells' functions will somehow be explained without having to think in terms of physical ensembles. **"This protein on one side of the [imaginary] cell membrane tugs on a protein on the other side," and then maybe the little homunculus who counts molecules will decide the time is right for him to carry a message to the correct gene to turn it on.**

It is probably true that a general picture can be completed after all of the details are present, but it isn't necessarily true that the specific interpretation will be meaningful. But at the present, we can see some of the meanings of the interaction between matrix and cell.

MUCUS, MUCINS, AND MYOPIA

The importance of carbon dioxide for respiration has been established, and its essentiality for even single-celled organisms has been reported. Whenever there is respiration, carbon dioxide is produced. By maintaining the effective concentration of Krebs cycle material, it protects the efficiency of respiration. Carbon dioxide is very soluble in water, but it is even more soluble in living tissue, so soluble that it will move from a low concentration in bath water into the body, where its concentration is already much higher.

Its high concentration in bone is not usually appreciated, but calcium carbonate is the form in which calcium is first deposited in new bone. Carbon dioxide reacts spontaneously with ammonia, and with other amines. The reaction of ammonia with carbon dioxide is the first step in the formation of urea, protecting against the potential toxicity of ammonia. Proteins probably bind a little more carbon dioxide on their amino groups than the amount that dissolves in a similar quantity of water, but biologists generally talk only about the carbamino content of hemoglobin, since the binding of carbon dioxide to this protein regulates the blood's ability to deliver oxygen to the tissues.

Carbon dioxide strongly influences the way in which water interacts with proteins, and it participates in the ability of iron-binding molecules to carry iron.

Although carbon dioxide probably associates with most of the amino groups in the body, only a few of these reactions have been studied. For example, it is known to bind to insulin, affecting its conformation. I think this is likely to explain some of the effects of the thyroid hormone in diabetes, since thyroid increases the production of carbon dioxide.

Mucins, or mucopolysaccharides, are combinations of proteins and polysaccharides, which make up a large part of the extracellular matrix; the blood–type substances are mucopolysaccharides, as are chondroitin and hyaluronic acid. The

carbohydrate chains of the mucins are made up of alternating sugars and amino sugars. When the amino groups are free, they will tend to associate with carbon dioxide, and so the way they interact with water, with each other, and with proteins, will be modified according to the amount of carbon dioxide present.

The simplest way to visualize the effect of carbon dioxide on mucopolysaccharides is to think of its action as an expectorant, in which it decreases the viscosity of bronchial mucus, allowing it to be reabsorbed or expelled. Since iodide also has a long history of use as an expectorant, we should compare the effects of carbon dioxide and carbonic acid with the effects of iodide in other situations.

The transparent structures of the eye are interesting places for considering the effects of carbon dioxide. I think carbon dioxide has a role in maintaining the clarity of the lens, as I discussed in the cataracts newsletter, **by preventing swelling**. The connective tissues of the eye's sclera and cornea are rich in mucopolysaccharides, and the vitreous body and the aqueous humor are very much like more dilute solutions of the same materials--the cornea is the most dense, and the aqueous is the most dilute. The fluidity of the aqueous is important because it circulates nutrients and oxygen from the blood, to sustain the lens and the cornea. The individual molecules in the aqueous are larger than those in the vitreous, but because there are fewer of them, the aqueous isn't very viscous. If carbon dioxide affects these molecules as it does the mucins in the bronchial secretions, then we can infer that it is important in maintaining the fluidity of the aqueous humor; **this would suggest that hypothyroidism, leading to a substitution of lactic acid for carbon dioxide, might contribute to the development of glaucoma by increasing the viscosity of the aqueous humor.**

Among mountain climbers, it has been reported that after staying several hours at a very high altitude, there is a decrease in the degree of myopia. Because of the Haldane-Bohr effect, in which carbon dioxide is retained when less oxygen is available, I think the high altitude effect on myopia involves a condensation of the connective tissue. In experimenters wearing gas tight goggles, and in scraped corneas kept in tissue culture, carbon dioxide has been found to have an **anti-swelling effect on the cornea.**

When rats have their thyroid glands removed, they become nearsighted, but if their pituitary glands are removed at the same time, they don't develop myopia. Hypothyroidism is classically associated with "myxedema," in which the tissues become overloaded with the glycoproteins or mucins. Several pituitary hormones are known to stimulate the overproduction of mucins.

In several of my classes, I asked students if they remembered when they became nearsighted. Although puberty is the usual time for myopia to begin, several girls mentioned that they had needed glasses within a month of beginning the oral contraceptive pill, and some of them found that their vision returned to normal when they stopped the pill, or began using thyroid supplements. High prolactin (associated with high estrogen or low thyroid) may be one of the factors in myopia.

Another experimental method for producing myopia is to cover the eye of a growing animal, or to keep the animal in constant darkness. In darkness, the eye grows larger than normal, causing the refractive error of myopia, and the sclera is soft and weak. Since stimulated nerves consume oxygen and emit carbon dioxide, I think darkness might mimic hypothyroidism, allowing the connective tissues to swell.

The sea cucumber has been used to study the physical properties of connective tissue, and it has been found that certain salts tend to soften the connective tissues, but that iodide doesn't. The well-established use of iodide to resolve granulomas, even when it doesn't eliminate the infectious agent, might suggest that it is protecting against something which is disrupting the connective tissue structure.

The only publications I have seen that presented clear evidence of the disappearance of arteriosclerosis involved treatment with iodides. In the retina, blood vessels can be seen to return to their normal appearance following a course of iodide treatment. Besides its possible direct effects on the mucins, iodide might help to

eliminate calcium from the walls of blood vessels, since calcium iodide is very soluble.

In aging, connective tissue becomes hardened by chemical cross-linking of the large molecules. If amino groups are well saturated with carbon dioxide, this type of reaction should be inhibited. (Carbon dioxide also inhibits the production of free radicals, which are involved in some types of cross-linking reactions.) The waterlogged condition seen during shock or stress in blood vessels, lungs, and other organs, and the edema of the brain and cataracts of the lenses that follow metabolic impairments of various sorts, seem to involve the uptake of "free" water, at the same time that "bound" (unfreezable) water is lost. Carbon dioxide seems to promote the retention of bound water, and protects against the edematous conditions. The swelling of muscles during hypoxic stress probably represents the basic process, in which lactic acid and pH increase, while CO_2 is lost.

Whatever the cell's "membrane" structure may be, Rothen's demonstration of the deep interactions of adjacent layers showed that the conditions on either side of the surface of a cell are very sensitive to conditions on the other side.

Since the mucopolysaccharides regulate cell division, cell shape and motility, cell longevity and cell death, and carbon dioxide has very powerful structural effects on the mucopolysaccharides, the cell, by producing carbon dioxide, is stabilizing its regulatory framework, the extracellular matrix, at the same time that it stabilizes the intracellular proteins and systems of metabolism..

The thyroid hormone is the most important promoter of carbon dioxide formation.

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attributable to sialic acid, chondroitin sulphates, hyaluronic acid, and heparan sulphate." "Cell growth was inhibited 40% when the fibroblasts were cultured on the fixed sheets of late passage cells. Treatment of the fixed cell sheets with heparitinase or nitrous acid resulted in complete recomvery from the growth inhibition. Cell growth on sheets of fixed cells derived from young, middle, and senescent fibroblasts showed that the surface of the senescent cells had the greatest inhibitory effect. These inhibitory effects of fixed cell sheets correlated well with both the amount of heparan sulphate relative to the total GAGs on the surface and to the saturation density of cell crowth at each passage. These findings strongly suggest that heparan sulphate, or its complex, on the cell surface in involved in the regulation of cell proliferation."

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"Modulation of protein tyrosine phosphorylation by the extracellular matrix," Corbett SA; Schwarzbauer JE J Surg Res, 1997 Apr, 69:1, 220-5 Fibronectin (FN) cross-linked to fibrin following injury provides the provisional matrix required for cells to begin tissue repair. Our previous work has demonstrated that fibroblasts adherent to multimeric FN within the context of a fibrin matrix (FN-fibrin) **exhibit clear phenotypic differences from those adherent to a dimeric FN-coated surface.** We hypothesize that this response to multimeric FN may be mediated by altered protein tyrosine phosphatase activity following integrin activation. Methods: NIH 3T3 cells were plated in the presence or absence of pervanadate (PV), a phosphotyrosine phosphatase inhibitor, on wells coated with FN or FN-fibrin matrix. Spread cell areas were measured after increasing incubation times and are recorded as mean cell area (mm2) +/- SEM. Alternatively, cells were lysed and equal amounts of protein were analyzed by immunoblot using a monoclonal antibody

specific for phosphotyrosine. Results: PV significantly inhibited cell spreading on FN-fibrin matrices. In contrast, PV treatment had little effect on cell area on FN alone. Analysis of cell lysates revealed that protein tyrosine **phosphorylation events differ in a substrate-dependent manner**. Conclusion: **Cell attachment to a FN-fibrin matrix induces distinct cell shape and cytoskeletal organization.** Inactivation of tyrosine-specific phosphatases enhances this distinction and inhibits the spreading of cells attached to this substrate. The phosphotyrosyl protein content of treated cells on FN-fibrin matrix is also diminished. These results suggest that **cell-extracellular matrix interactions affect the tyrosine phosphorylation balance of the cell, thus modifying cytoskeletal organization** and related signaling events."

"Inhibition of anchorage-dependent cell spreading triggers apoptosis in cultured human endothelial cells," Re F; Zanetti A; Sironi M; Polentarutti N; Lanfrancone L; Dejana E; Colotta F Borgomainerio, Milano, Italy. J Cell Biol, 1994 Oct, 127:2, 537-46 When cultivated on substrates that prevent cell adhesion (the polymer polyhydroxyethylmethacrylate, bovine serum albumin, and Teflon), human endothelial cells (EC) rapidly lost viability with a half-life of approximately 10 h. Dying EC showed the morphological and biochemical characteristics of apoptosis. The apoptotic process of suspended EC was delayed by the protein synthesis inhibitor cycloheximide. To obtain information as to the mechanism involved in the apoptosis of suspended EC, we investigated whether **adhesion to matrix proteins or integrin occupancy in EC retaining a round shape** may affect EC suicide. EC bound to **low coating concentration** of either fibronectin or vitronectin, **retaining a round shape and failing to organize actin microfilaments, underwent to rapid cell death;** by contrast, cells on **high substrate concentrations became flattened, showed actin microfilament organization,** and retained viability. Addition of saturating amounts of soluble vitronectin to suspended round-shaped EC did not reduce the process of apoptosis. Finally, when suspended EC bound Gly-Arg-Gly-Asp-Ser-coated microbeads (approximately 10 microbeads/cell), yet retaining a round shape, the apoptotic process was not affected. Oncogene-transformed EC in suspension were less susceptible to cell death and apoptosis than normal EC. Overall, these data indicate that cell attachment to matrix or integrin binding per se is not sufficient for maintaining cell viability, and that cells need to undergo some minimal degree of shape change to survive. Modulation of interaction with the extracellular matrix can, therefore, be an important target for the control of angiogenesis.

"EFFECT OF CARBON DIOXIDE ON THE THERMODYNAMIC STATE OF WATER IN COLLAGEN," JOURNAL OF FOOD SCIENCE 53(4). 1212-1215, 1988. "Thermodynamic activities of polar sites of collagen in the presence of CO2 were observed by inverse gas chromatographic techniques using water as a probe. The interactions between collagen and the water probe were evaluated by determining the specific retention volume (Vg.degree.) and partition coefficient (Kp) at 25.degree. C, 30.degree. C, and 35.degree. C. Thermodynamic parameters were determined from these data. CO2 exhibited a significant effect on the water binding of collagen as shown by increased Vg.degree. and Kp values as compared to N2- and He-treated collagen. The thermodynamic parameters of partial molar Gibb's free energy...partial molar enthalpy...and partial molar entropy**...indicated CO2 significantly increased the average energy of water binding by collagen."**

Kinetics of decreased LPS-stimulated cytokine release by macrophages exposed to CO2. West MA; Baker J; Bellingham J, J Surg Res, 1996 Jun, 63:1, 269-74. **"The mechanisms responsible for the lack of inflammation after laparoscopic surgery remain unknown. Peritoneal macrophages (M phi) incubated in carbon dioxide (CO2) but not air or helium (He), had significant, reversible inhibition of lipopolysaccharide (LPS)-stimulated tumor necrosis factor (TNF) and interleukin-1 (IL-1)** release. In these experiments the kinetics of these C02-induced alterations in cytokine secretion were examined. Murine peritoneal Mphi were stimulated with LPS for 4 hr and incubated in different test gases (95% air/5% CO2,80%CO2/20%O2,80% He/20% O2) for intervals between 0.25 and 4 hr. Time between gas incubation and LPS stimulation was varied to determine the persistence of CO2 inhibition. Parallel M phi groups received LPS stimulation 24 hr later. Supernatant TNF and IL-1 were measured by bioassay and polymerase chain reaction was used to examine cytokine mRNA. Significant reversible inhibition of TNF and IL-1 was seen with CO2, but not He or air. **Inhibition of IL-1 occurred 15 min after CO2 exposure,** was associated with decreased IL-1 mRNA, and was rapidly lost following incubation in the control atmosphere. TNF inhibition was seen despite normal levels of TNF message, required more than 30 min of CO2 exposure, and persisted after CO2 removal. **CO2 produced profound, reversible, inhibition of LPS-stimulated cytokine release by peritoneal Mphi. The transient inability to secrete inflammatory cytokines after CO2 exposure may explain the lack of systemic inflammation after laparoscopic surgery with CO2."**

"Do plasma and serum have different abilities to promote cell growth?" Gospodarowicz D; Ill CR Proc Natl Acad Sci U S A, 1980 May, 77:5, 2726-30 "The abilities of plasma and serum to support the growth of vascular smooth muscle cells maintained on uncoated tissue culture dishes or dishes coated with an extracellular matrix (ECM) have been compared. Vascular smooth muscle cells maintained on plastic dishes and exposed to plasma proliferate poorly; when exposed to serum they proliferate actively. Addition of fibroblast growth factor (FGF) incrases the growth rate of the cultures in both cases. In contrast, when vascular smooth muscle cells are maintained on an ECM, they proliferate

equally well exposed to either plasma or serum. Because the cultures had an average doubling time (15 hr) that was already at a minimum, FGF no longer had an effect on vascular smooth muscle cell proliferation." "These results raise the possibility that the lack of response of vascular smooth muscle cells, as well as that of other cell types in vitro, to plasma factors is **not an intrinsic property of the cells but is rather due to the substrate upon which the cells rest. Because cells maintained on an ECM respond to plasma factors, it is likely that the close contact of the cells with the ECM restores their sensitivity to physiological factors present in plasma."**

"Factors controlling the proliferative rate, final cell density, and life span of bovine vascular smooth muscle cells in culture," Gospodarowicz D; Hirabayashi K; Giguère L; Tauber JP J Cell Biol, 1981 Jun, 89:3, 568-78 "Low density vascular smooth muscle (VSM) cell cultures maintained on extracellular-matrix(ECM)-coated dishes and plated in the presence of either plasma or serum will proliferate actively when serum-containing medium is replaced by a synthetic medium supplemented with three factors: high density lipoprotein (HDL, 250 micrograms protein/ml); insulin (2.5 micrograms/ml) or somatomedin C (10 ng/ml); and fibroblast growth factor (FGF, 100 ng/ml) or epidermal growth factor (EGF, 50 ng/ml). The omission of any of these three factors from the synthetic medium results in a lower growth rate of the cultures, as well as in a lower final cell density once cultures reach confluence. When cells are plated in the total absence of serum, transferrin (10 micrograms/ml) is also required to induce optimal cell growth. The effects of the substrate and medium supplements on the life span of VSM cultures have also been analyzed. Cultures maintained on plastic and exposed to medium supplemented with 5% bovine serum underwent 15 generations. However, **when maintained on ECM-coated dishes the serum-fed cultures had a life span of at least 88 generations. Likewise, when cultures were maintained in a** synthetic medium supplemented with HDL and either FGF or EGF, an effect on the tissue culture life span by the substrate was observed. Cultures maintained on plastic underwent 24 generations, whereas those maintained on ECM-coated dishes could be passaged repeatedly for 58 generations. These experiments demonstrate the influence of the ECM-substrate only in promoting cell growth but also in increasing the longevity of the cultures."

"Determination of cellular shape by the extracellular matrix and its correlation with the control of cellular growth." Gospodarowicz D; Greenburg G; Birdwell CR Cancer Res, 1978 Nov, 38:11 Pt 2, 4155-71 **"Although the problem of cellular proliferation may seem at first glance to be tremendously complex, the mechanisms which control it may be extremely simple. One of the primary factors which regulates the mitogenic response of a given cell type to a given class of mitogenic agents seems to be the cellular shape.** We have found that corneal epithelial cells, for example, adopt a flattened configuration when maintained in vitro on plastic and are very sensitive to fibroblast growth factor, but not to epidermal growth factor. When maintained on collagen, on the other hand, they become tall and columnar and respond primarily to epidermal growth factor. The cellular shape is dictated in vivo by the extracellular material upon which the cells rest and in vitro by the substrate upon which the cells are maintained. The substrate itself may, in turn, induce the cells to manufacture their extracellular material and specific cell surface proteins which control the cellular shape."

"The control of mammalian cell proliferation by growth factors, basement lamina, and lipoproteins. Gospodarowicz D J Invest Dermatol, 1983 Jul, 81:1 Suppl, 40s-50s "The effect of growth factors such as fibroblast growth factor on the production of a basement lamina by cultured endothelial cells has been investigated. The ability of these cells to grow and differentiate properly correlated with their ability to produce a basement lamina. The effect of such a substrate on the growth, differentiation, and aging of cells in vitro, as well as its use for the long-term culture of either normal diploid cells or tumor cells, is reviewed.

Effect of high and low density lipoproteins on proliferation of cultured bovine vascular endothelial cells." Tauber JP; Cheng J; Gospodarowicz D J Clin Invest, 1980 Oct, 66:4, 696-708 "Bovine vascular endothelial cells maintained on dishes coated with an extracellular matrix and exposedto medium supplemented with lipoprotein-deficient serum (LPDS) require the presence of lipoprotein to proliferate optimally. High density lipoprotein (HDL) seems to be the major factor involved in the proliferation of vascular endothelial cells. This is mostly due to its lack of toxicity when added at high concentration, as well as to its nondependence on LPDS to exhibit its mitogenic properties. Therefore, HDL hysiological concentrations (1,000--1,500 microgram protein/ml) can fully replace serum. Low density lipoprotein, unlike HDL, has a biphasic effect. Although mitogenic for vascular endothelial cells when added at low concentration, once physiological concentrations are reached it becomes toxic for the cells. Moreover, and in contrast with HDL, the mitogenic effect of low density lipoprotein was found to be a function of the LPDS concentration to which cultures were exposed. The substrate upon which cultures are maintained has been found to be an important factor if a mitogenic effect of HDL is to be observed. When maintained on plastic, cells proliferate poorly in response to HDL unless fibroblast growth factor is added to the medium. **In contrast, when maintained on extracellular matrix, an optimal growth rate is induced by HDL, even in the absence of fibroblast growth factor.** This **suggests that, in vivo, the integrity of the basement membrane upon which endothelial cells rest and migrate is an important factor in determining the cells response to lipoproteins present in plasma. "**

si sel il s'avoue par besoin de surrenales
le sel ultra important pour recharger les surrenales
Prog régularise le niveau de sodium

Ray Peat's Newsletter

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Le stress ultime c'est le shock. Pour pas mourir il faut ↑ energie

Recharging the System

Adelle Davis wrote about the importance of increased salt intake in adrenal failure, and animal experimenters have demonstrated that with adequate sodium and sugar, animals can function normally without their adrenals. Hans Selye demonstrated that progesterone supplements keep animals healthy for their entire life after their adrenals have been removed. Among its many effects, progesterone regulates the levels of sodium and glucose.

Progesterone is both an antistress hormone and an antishock hormone; shock is the state that occurs when our defenses are down, and stress is just a little higher on the scale of resistance, and neither will occur when our resources are adequate. In any bad biological situation, estrogen is likely to accumulate, interfering with energy production, causing blood to pool in the legs, causing water retention and sodium loss.

> "The essence" of shock "seems to be a relative disappearance of blood from the heart and great vessels, so that the heart has not sufficient fluid on which to contract. Much used to be written about 'the mystery of the lost blood.'" W. Boyd, A Text-Book of Pathology, 1943.

Thyroid, progesterone, protein, and salt are powerful defenses against all sorts of stress-associated symptoms, including hot flashes, insomnia, cramps, PMS, edema, toxemia of pregnancy, low-birth-weight babies, epilepsy, heart diseases, hypertension, strokes, migraine, inflammatory diseases, hypoglycemia, fatigue and depression. The first approach to an appropriate diet would be to use **at least** a quart of milk and a quart of orange juice daily, well salted chicken broth, and frequent snacks, especially salty foods. I have written before about the importance of fruit and protein in balancing the hormones, and how adequate energy prevents stress, but I haven't talked about sodium's central biological role in sustaining our energy, and the mechanisms behind these effects of diet and hormones..

Shock is the most extreme stress-state there is, and it can shift gradually into death, as energy production ceases. Things that can bring an individual out of shock are so intimately connected with our energy production that we should understand how to use them routinely.

In shock, G. W. Crile showed that many systems, ranging from the molecular level to the nervous level, are involved, and he introduced methods of anesthesia that reduced shock. He imagined the organism--and each cell--as something like an electrical battery: The liver and the brain formed the poles of the organism-battery, and the nucleus and cytoplasm formed the cell's "poles." Exhaustion and shock, he believed, in some way "discharged" the organism's energy, causing changes in every cell.

> "The use of CO2 for synthetic purposes by the mammalian cell is now being studied in detail; it has already taken on tremendous significance since it completely reverses the hitherto firmly accepted view that CO2 is merely a waste product of animal metabolism. R. Levine, "Carbohydrate Metabolism," in Diseases of Metabolism, G.G. Duncan, ed., 1964.

I suspect that Crile's work on the physiology of excitement, exhaustion, and shock made Hans Selye's work on stress and adaptation "less unacceptable" to the scientific establishment than it

Shock state = l'humain n'a plus de défense
thy + Prot + Prog + sel protège contre le stress

Pour traiter le shock : Sodium, Glucose, ATP injectable, antago de morphine
Naloxone

would have been without Crile's disturbing precedent. Crile warned about the shock-promoting action of morphine, and influenced the way surgery was done, but unfortunately shock is still too often thought of in a mechanical way, as something that happens to the circulatory system, and the various subsequent discoveries about treating shock have seemed too mysterious or too implausible to gain general acceptance. In the absence of a unifying picture of the organism, treatments are likely to be evaluated in terms of a fragmented aspect of the organism, and if they don't mechanically fit into that system in an obvious way, they are dismissed.

I have written previously about several dramatically effective treatments for shock that were developed in the last fifty years--for example, intravenous ATP, concentrated solutions of sodium chloride or glucose, and the morphine/endorphin-blocker, naloxone. Theoretical reasons have kept some of these techniques from being used as widely as would be appropriate, but gradually the success of the methods is forcing some people to rethink their theories.

A simple newer view of the organism's energy is being developed, and early acceptance of this new view will make it possible to approach treatment in a way that is both integrated and specific.

Although Crile and Selye were famous for their studies of the acute effects of noxious conditions, both were interested in the long-term, cumulative effects. Crile was more explicit about the general evolutionary implications of his discoveries.

One of the least scientific aspects of conventiional "evolutionary thinking" is the thought that if an organism has or does something, that thing or behavior must have "survival value." People apply evolutionary explanations in a carefree way, feeling that an explanation without factual support is better than leaving something unexplained.

Shock, inflammation, aging and death have been proposed to "have survival value," because of this totalitarian view of genetics. Couldn't it be that organisms simply aren't perfect, and that some things are just systematically screwed up? That is, an organism has a certain strength, resistance, or adaptive capacity, but if it finds itself in conditions that are too difficult, then processes that never did anything to aid survival might develop, as several individually valid defensive maneuvers start to interfere with each other. "Advance" and "retreat," eat and expel, for example, are processes that have to be functionally separated; if coordination is lost, new but confused processes will emerge. On the cellular level, excitotoxicity is an example of the loss of coordination.

In 1950 Selye, and in 1953, Rees, pointed out the similarities of estrogen's effects to the physiology of stress and shock. Hundreds of studies have confirmed the details of estrogen's actions on the circulatory system, respiration, and metabolism. Since we have the genes needed for making estrogen, it might seem that there is reason to argue that shock "has a genetic basis," but the mistake occurs when that phraseology is extended to claim that "genes for (something which produces) shock prove that shock has survival value." Estrogen's survival value exists only in the context of a whole organism with multiple ways for limiting estrogen's destabilizing actions. Estrogen's harmful effects occur when our systems for opposing it fail.

Recently, there has been a dispute about the reason for the evolution of menstruation among primates. The argument began when Margie Profet proposed that it is an anti-infective defense mechanism, a "cleansing" procedure. Culturally, this strikes me as primarily a reaction against the archaic doctrine of the "unclean" menses, and scientifically, it is hard to imagine that opening blood vessels and bathing the membranes in blood would be an anti-infective strategy; in fact, infections such as gonorrhea and chlamydia are more likely to occur after menstruation, and blood is an exceedingly good growth medium for germs. Her

> Cramps, insomnia, shock, heart attacks, and many other problems could be seen as consequences of a general energy problem, if it weren't for a few dogmatically fixed ideas that are held in place by academic/bureaucratic defensiveness and arrogance. "Membranes" and "membrane pumps" are more important than (other people's) life to these dogmatists.

response to that observation was that the prevalence of diseases such as AIDS, cholera, and tuberculosis "doesn't mean that the immune system didn't evolve to fight pathogens." I think she is wrong on both issues, the reason for evolving menstruation and the reason for evolving our immune system.*

If we can see menstruation as a side effect of the adaptations we have for producing large brains, without its own special "menstruation genes," we should also be able to see a phenomenon such as shock as something which is not biologically so useful that we "evolved" it in the sense of selecting for "shock genes." (Stumbling is a consequence of walking, and the biological point of interest is the walking, not the stumbling; any interest that stumbling has, is as a "boundary" of the ability to walk.)

My point is to suggest that shock is simply a negative thing, a failure of protective systems, a biological screw-up resulting from the same sort of inadequacy of resources that produces "excitotoxicity." *The fact that shock-like features can be seen in the hormonal effects of estrogen, and in the "normal" process of aging, leads to the thought that the body which can control the effects of estrogen should also be able to control the shock reaction and the aging process, if given the appropriate kinds of support.* Estrogen creates a bias toward cellular "excitotoxicity," since it promotes excitation while limiting energy production. Our body controls estrogen's effects by decreasing excitation while increasing efficient energy production.

The several effective methods of preventing death from shock can give us insight into this general process of the failure of life, and so into the nature of life itself.

The average biology professor is just about as unsophisticated as the average television-viewer about water in organisms--how it got there, why it stays there, what it does. The typical biologist maintains the conventional view of the cell by changing the subject whenever a fact conflicts with a doctrine. The history of the "cell membrane" shows how this mental process has worked.

At first, an oily coat was thought to account for the different composition of the watery solutions around cells, and inside cells. Then "membrane pumps" were introduced to explain the differences, because too many facts were inconsistent with the simple membrane idea. Proteins were found and identified as the pumps. Then it turned out that pumps would require energy that cells couldn't (and needn't) provide, and many ways were devised to explain the minimal energy needed to maintain the composition of cell water. But the "pump-proteins"--calcium-ATP-ase, sodium/potassium ATPase, etc.—are proteins that really exist, though their functions are much more interesting than "pumping." An important context for thinking about these ATPases is that the contractile protein of muscle (myosin) is a calcium-dependent ATPase.

The habit of biochemists has been to think of enzymes as the soluble proteins that could be extracted from cells in a watery solution, and to ignore the insoluble residue, which contained the ATPases. Now, much of the residue has been resurrected for biochemistry, under the name of "membrane proteins." The "ghost" of the red blood cell, after it has been shocked into losing its hemoglobin, is a popular lab preparation that biochemists like to call a "membrane," though the term is grossly misleading. Szent-Gyorgyi, Gilbert Ling, and a few physically conscious biologists spoke of these relatively insoluble proteins as structural proteins.

In 1968 or '69, I had been reading the previous 50 years of research on cell physiology, and I saw that for 20 years, Gilbert Ling had been almost alone in offering a view of the cell that was physically possible. He had solved the problems of ionic regulation in ways that physical chemists could accept, but biologists were proceeding as if his solutions to their problems didn't exist. I wrote to him, to see if I, as a newcomer to "science," was missing something. He said that I just didn't understand what "science" was; it was a matter of money, prestige, and influence, with little concern for what was true.

It has been calculated that the substances which are distributed unequally between cells and

the surrounding fluid would require 15 times as much energy as the cells can produce, if their distribution had to be maintained by pumps, but it has also been demonstrated that cells can remain almost at equilibrium, when their energy production is completely blocked by poisons. **Something maintains the ions and other solutes in their unequal distribution between the inside and outside of the cell, but it doesn't take energy to do it. This is why cells have been compared to ion-exchange resins, which also have the ability to passively select certain ions while excluding others.** People who have examined the atom-by-atom physics of how an ion-pump might work have demonstrated the silliness of the idea. Ion-exchange granules selectively bind certain ions that reach them by passive diffusion, and similar near-equilibrium processes can account for the ion gradients maintained by cells. The interesting difference in cells (compared to ion-exchange resins) is that their physical near-equilibrium is closely balanced with chemical processes, which are also much closer to equilibrium than conventional schemes imagine.

From observing the retarded relaxation of muscles in hypothyroidism, it is clear that low energy makes relaxation difficult.

Szent-Gyorgyi showed that muscle in rigor mortis softened when placed in ATP solution.

The failing heart becomes stiff.

Stretching a muscle increases its ATP.

Increasing the concentration of sodium, ATP, carbon dioxide, ... in the cell's environment increases its ATP content.

Filling the heart stretches it, increasing its ability to beat.

Understanding the silliness of the "pump" idea demystifies the membrane idea, and then a person can begin to think about how cells really work.

Stimulated, active cells expend energy. Besides doing measurable work, such as contraction, they release a measurable amount of heat, at the moment of responding to stimulation. Surprisingly, stimulated nerves have been observed to absorb heat immediately after releasing it, in a "refrigerator-like" process that coincides with their electrical repolarization. No one was able to explain this on the basis of membranes and pumps, since the pumps should be releasing their heat *after stimulation and during repolarization.*

I have thought of this in terms of Kelvin's idea of increased surface area leading to decreased temperature. What we need, in order to understand the way energy can be used in reestablishing the cell's resting condition without releasing heat, might be the idea that physical processes (the change of protein conformation and water structure) are intimately integrated with chemical equilibria.

Around 1970, a famous English researcher was in Eugene lecturing about his theory that the famous "high energy bond of ATP" (14 kcal, I think he said) could be used to explain muscle contraction. I had just read an old paper by one of my professors, Sidney Bernhard, which showed that its bond energy wasn't nearly so high. When I asked Bernhard why "everyone talks about ATP's high-energy bond," he just said "everyone doesn't."

When ATP breaks down it absorbs water, and when it is synthesized, water is released. In a water-free environment, the equilibrium favors the formation of ATP. The chemical activity of water in cells is lower than it is in ordinary water. Given the right (anhydrous) environment, ATP will form spontaneously. As the reactants form ATP and give up water, energy is (at least theoretically) absorbed by the chemical bond. In the abstract, this shows that the formation of ATP and the absorption of energy could be caused by factors that control the activity or availability of water. The protein-ATP complex is one of those water-regulating factors.

The abstract idea that ATP could be formed spontaneously by a "relaxing" cell (recovering from stimulation) goes against the idea that a "cell is a motor and ATP is the fuel." Some people have argued that the contraction occurs first, causing ATP to be split, rather than the reverse. Other examples of enzyme activation support this view, that the contraction or activation is a physical process, like releasing a spring. In the contracted

or activated state, sodium is able to enter the cell momentarily, and the presence of sodium seems to allow the ATP to be reformed. **These differences might seem subtle, but they have made an all-or-none difference in the minds of medical people deciding on therapies and diets.**

This picture of a cell as a loaded spring, or as analogous to the ion exchanger in a water-softener, is the sort of image I have in mind when I speak of "charging the system."

Several researchers have demonstrated that intravenous injections of ATP prevent death from shock, that shock depletes the ATP of the cells, and that depleted cells absorb ATP much more readily than normal cells that don't lack it. All of the biologists and biochemists (at Oregon's Institute for Molecular Biology) that I mentioned this to said it was impossible, "because ATP is highly ionized and can't cross the cell membrane."

Even when a general idea is clear and consistent with the facts, if it opposes the dominant view it needs some experiments that can hardly be understood without it.

Liver ATP is increased as a result of increasing blood sodium. An increase of only about 15% in the blood sodium, for example, caused the cells' ATP to nearly double. [R. L. Veech, et al., "Relationship of free cytoplasmic pyrophosphate to liver glucose content and total pyrophosphate to cytoplasmic phosphorylation potential," FEBS Lett. 117, K65-72, 1980.]

Sodium is an "extracellular" ion, one that binds water to itself so strongly that it is excluded from the cell under normal conditions, in which the water is dominated by the cell's structural molecules. It is only when the cell is stimulated or fatigued that it absorbs larger amounts of sodium, and the fatigued cell also absorbs an excess of water. The textbooks say "water follows sodium," but the physical reality is that sodium also follows (free) water, and that it tends to be excluded from the water of cells. **Increasing the sodium in the environment of a water-logged cell will tend to dehydrate the cell.**

This experiment, using sodium to increase ATP (especially when we remember that ATP is an effective treatment for shock) shows how hypertonic sodium might rescue a shock victim, increasing circulatory efficiency, helping to increase blood volume, restoring the cell's electrical and chemical resting state, and possibly regulating intracellular pH. [G.. B. Haycock, "The influence of sodium on growth in infancy," Pediatr. Nephrol. 7(6), 871-875, 1993.] The increasing blood volume is a "mechanical" effect that helps to make the use of hypertonic sodium culturally more acceptable, but it is really secondary to the other effects of sodium. The first water to be restored to the serum is that contained in red blood cells and the swollen endothelium. *Capillaries and small blood vessels that have been obstructed by swollen endothelial cells allow free passage of the blood, and the increased water lowers the blood's viscosity, improving its ability to deliver oxygen and glucose.* Brain swelling is reduced, and consciousness is restored. Glucose metabolism is also improved under these conditions.

Sodium causes the ATPase to produce ATP, rather than consuming it. (P.J. Garrahan and I. M. Glynn, "The incorporation of inorganic phosphate into adenosine triphosphate by reversal of the sodium pump," J. Physiol. 192, 237-256, 1967.; P. A. Dibrov, et al., "A study on Na+-coupled oxidative phosphorylation: ATP formation supported by artificially imposed delta pNa and delta pK in Vibrio alginolyticus cells," J. Bioenerg. Biomembr. 21(3), 347-357, 1989.)

The membrane-pump theory says that the cell *consumes* ATP to expel the sodium which enters, and increased external sodium increases its likelihood of entering the cell, but in reality increased external sodium causes more ATP to be produced. **The precise balance of ions seems to make the difference between consumption or production of ATP.** [L. Plesner, et al., "[32P]ATP synthesis in steady state from [32P]Pi and ADP by Na+/K+-ATPase from ox brain and pig kidney. Activation by K+," Biochim. Biophys. Acta 1040(2), 167-174, 1990.]

Remembering that the muscle protein is an ATPase, there is a situation that I think is analogous. When a muscle is stretched, it forms ATP, rather than consuming it. This could be the result of a slight change in the physical state of the water and small changes in chemical affinities produced

Sodium act anti-adrenaline ↑ glucose down cell ↑ choles

by the changes in protein conformation. Before this effect of stretch on ATP synthesis was directly observed, Starling's law of the heart recognized that the force of contraction increased with the initial length of the muscle fiber. Simply increasing blood volume increases the effectiveness of the heart contraction. Szent-Gyorgyi described a related process (the "staircase" phenomenon) as "function building structure, structure producing function."

Sodium is required for cells to absorb glucose and amino acids. I have recommended salty foods at bedtime to promote sleep, because of sodium's recognized anti-adrenalin effect. There are some complicated ways of thinking about its effect on adrenalin, as there are for explaining its thermogenic effect, but the simple fact that it is needed for absorbing glucose can explain its ability to lower adrenalin (since adrenalin rises when glucose is needed) and to increase heat production.

In the fetus and the newborn baby, sodium promotes growth. Progesterone, sodium and glucose are often limiting factors in the growth of the baby's brain; when they are deficient, cells die instead of growing.

The fact is that sodium energizes. It helps to remove calcium from the cell, to produce ATP, and to promote absorption of glucose and amino acids. The fear many physicians have of injecting hypertonic sodium chloride is odd, in the light of the knowledge that has accumulated in recent decades. Chloride isn't always the ideal anion, but more elaborate preparation is needed for providing the ideal ionic solution.

Carbon dioxide is powerfully involved in the regulation of both sodium and calcium, as well as in respiration and energy production.

It tends to relax both nerves and muscles. It is apparently one of the essential factors in preventing edema. [For example, in the cornea; M. V. Riley, et al., 1995.]

ATP and CO2 both bind to hemoglobin, regulating its affinity for oxygen. The way in which they bind to this protein indicates that they will bind to many other intracellular proteins, similarly regulating the functions of those proteins.

The elimination of water from the environment in which ATP is formed or decomposed favors its formation, and in this environment ATP doesn't contain its reputed "high energy bonds," but it still has its strong affinity for binding to proteins. Sodium binds water to itself, and it is this feature that leads to its exclusion from the normal cell. CO2, when it is in water, especially with the carbonic anhydrase enzymes, combines with water. As it is formed in the mitochondria, this means that it will carry water (as well as calcium and sodium) out into the cytoplasm, and out of the cell.

In many situations, including brain hypoxia, carbon dioxide is the decisive protective factor.

Low thyroid function involves reduced formation of carbon dioxide, and the body fluids don't retain as much sodium as in normal individuals. Both urine and sweat tend to contain abnormally high sodium concentration in hypothyroidism. Because CO2 is central to the regulation of pH, and hydrogen ion excretion (acid urine) is one mechanism involved in sodium retention, the CO2 deficiency of hypothyroidism is probably closely connected with the inability to retain adequate sodium.

The body fluids are actually hypotonic in hypothyroidism.

If hypertonic sodium energizes, then the low-sodium hypoosmotic fluids of hypothyroidism de-energize.

Low-thyroid cells are also unable to retain magnesium efficiently, and a magnesium deficiency prevents muscle relaxation, wasting energy. Adequate sodium prevents urinary magnesium loss.

Hypothyroidism tends to cause hypoglycemia, and the lack of glucose (even if it is because the glucose in the blood can't be absorbed because of insufficient sodium) causes elevation of adrenalin. Hypertonic sodium given intravenously lowers the amount of adrenalin in the blood, just as the thyroid hormone does.

Hypothyroidism also causes an imbalance between the antiestrogenic antishock hormones, progesterone and pregnenolone, and proshock estrogen.

The close integration of physical and chemical processes when those processes are near

equilibrium is the fact or the principle that is lacking in the doctrine that the cell is like a collection of motors, fueled by ATP. If you can imagine a Chevrolet that at times creates gasoline while absorbing heat, then the simile would be acceptable. The inappropriateness of the mental image of a cell with pumps and motors leads to the treatment of shock with things that produce shock, of heart failure with things that produce heart failure, and of aging with things that accelerate aging.

NOTE: *The estrogen dominance which is needed to start the reproductive cycle, with cell proliferation in the endometrium, breast, and pituitary, is not otherwise useful to the organism, and is controlled and opposed during pregnancy by a constantly rising production of progesterone. The state of estrogen dominance is essentially unstable. P. T. Ellison, emphasizing the "energy hungry brains" of primates, explains the need for the massive endometrial growth in primates, and Strassman observes that endometrial regression occurs in all mammals. These are important points. Their failure to point out that estrogen has many undesirable systemic effects very likely results from the cultural context that has been created by the estrogen-promoting pharmaceutical industry.

The group of processes that we call the immune system is so deeply integrated with everything else in the organism that to talk about "the reason for evolving it" is as misleading as to talk about "the reason" for evolving certain pigmentations–black feathers, for example, are mechanically stronger than white ones, selection of foxes for domesticability changes their fur pigmentation and their voice, selection for egg laying somehow produces suppression of feather pigmentation, etc., yet people like to talk about protective coloration, because an easy connection can be made between that and genetic selection. Being an organism is a problem whose solution may require inventive use of internal and external resources; chromosomes are internal resources, not clusters of traits.

The ideology that sees the organism as a sum of traits, each with its gene, has been a failure in providing understanding about how an organism comes to exist.

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SAMPLE

Ray Peat's Newsletter

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Regeneration and the Anti-adaptogens

I don't think aging is necessary, and I think I have begun to see the organism in a context that can explain the cause of aging in a relatively simple way.

In outline, this is how I see it:

1. Every cell and tissue is capable of renewal;

2. the (Hayflick) doctrine of absolutely limited cellular renewal capacity has been disproved in many ways;

3. the great variety of degenerative diseases which can be promoted by a few factors--radiation, oxygen deprivation, polyunsaturated fats, and estrogen--can serve as a guide to the nature of our basic control systems;

4. the factors which disrupt our natural regulatory systems contain clues to possible restorative methods.

Every important issue in life is an opportunity for powerful self-interest to intervene and take control. In transportation, corporations interested in selling gasoline and cars destroyed the cities' elegant systems of electric trolleys, in energy the nuclear and petroleum interests fought the development of solar and wind power, and the timber industry lobbies against innovation in house construction. The issue of aging and death is one that has been consciously dealt with throughout human existence, and it has accumulated a most complex system of mental commitments. This investment of emotion and belief affects every aspect of theory and practice in biology and medicine. We have to keep asking "is this researcher ignoring some facts that might seem to conflict with his ideology?"

Definitions:

Hayflick limit: Leonard Hayflick found that certain animal or human cells which can be grown in a dish would die out after 50 divisions, and he announced that this limited ability to divide sets the maximum limit of the lifespan. He has said that this is governed by the principle that entropy tends to increase. Another group found that the same kind of cell continued to divide nicely after 110 divisions, and didn't begin to die out until they began to use the serum from a different calf. The cells of the skin and bowel divide thousands of times in a normal lifetime, and transplanted pieces of skin or mammary gland remained healthy through the lifetimes of ten animals in series.

Telomere: A structure on the ends of chromosomes that gets shorter with each division in some cells. The enzyme telomerase reconstitutes the telomeres in "immortal cells," such as germ cells and cancer cells. In aging, most aspects of cell function are weakened, but this particular enzyme operates in a location close enough to "the genes" that some people think it is behind the "Hayflick limit." But many other repair systems also slow down with aging; nothing gives this structure special explanatory power.

Previously, I have talked about the doctrine that our cells are divided into the immortal cells of "the germ line," and the mortal "somatic" cells of all the rest of the body. This doctrine says "people

are mortal, so their cells must be intrinsically mortal, but they can have descendants ad infinitum, so their germ cells must be different from all the rest of their cells, and immortal." Alexis Carrel was famous for demonstrating that heart cells could be immortal in the right environment, but his work is now ignored or dismissed. "Only cancer cells and the germ line are immortal," the present doctrine says; ("and maybe embryonic cells"). It seems that the immortalization of our mortal somatic cells is acceptable, as long as these cells have the function of killing us.

I think some of Carrel's ideas about the nature of living organization and of aging are worth quoting. (Man the Unknown, 1935.)

"Isolated cells have the singular power of reproducing...the edifices characterizing each organ. If a few red corpuscles, impelled by gravity, flow from a drop of blood placed in liquid plasma and form a tiny stream, banks are soon built up. Then, these banks cover themselves with filaments of fibrin, and the stream becomes a pipe, through which the red cells glide just as in a blood vessel. Next, leucocytes come, adhere to the surface of the pipe, and surround it with their undulating membrane. The blood stream now assumes the appearance of a capillary vessel enveloped in a layer of contractile cells. Thus, isolated red and white corpuscles manage to construct a segment of circulatory apparatus, although there is neither heart, circulation, nor tissues to be irrigated." "The spontaneous tendency toward formation of the organs by their constitutive cells, like the social aptitude of the insects, is a primary datum of observation." (Page 107.)

"The simplest system, where the phenomenon of sensescence is observed, consists of a group of tissue cells cultivated in a small volume of nutritive medium. In such a system, the medium is progressively modified by the products of nutrition and, in its turn, modifies the cells. Then appear senescence and death. The rhythm of physiological time depends on the relations between the tissues and their medium. It varies according to the volume, the metabolic activity, the nature of the cell colony, and the quantity and the chemical composition of the fluid and gaseous media. The technique used in the preparation of a culture accounts for the rhythm of life of such culture. For example, a fragment of heart fed with a single drop of plasma in the confined atmosphere of a hollow slide, and another one immersed in a flask containing a large volume of nutritive fluids and gases, have quite different fates. The rate of accumulation of the waste products in the medium, and the nature of these products, determine the characteristics of the duration of the tissues. When the composition of the medium is maintained constant, the cell colonies remain indefinitely in the same state of activity." "If, by an appropriate technique, their volume is prevented from increasing, they never grow old. Colonies obtained from a heart fragment removed in January, 1912, from a chick embryo, are growing as actively today as twenty-three years ago. In fact, they are immortal." (Page 173.)

Heart cells are recognizable even in isolation, because they beat. It would be impossible to mistake them for another type of cell.

Years later, Hans Selye was observing the reaction to a small glass tube inserted under a rat's skin. He noticed that the tube was soon enclosed by a capsule of fibrous tissue, and that the cells gradually grew in a strand from the ends down the channel of the tube. These cells were isolated from the fluids that normally surround cells, and Selye found that after a short time they took on the appearance of cells from a very old animal, while the cells of the surrounding capsule remained normal. Selye drained the fluid at intervals, allowing it to be replaced by fresh fluid, and found that at the end of the rat's life-span, the cells of this filament showed no signs of aging.

Carrel's work with tissue-culture led him to believe that changes in the organism's fluids were a major part of the aging process. Extracts from animal embryos have been used medically for treating old people, because of their confirmed effect on cell function. "Blood plasma alone displays, throughout the entire life-time, progressive modifications characterizing the senescence of the body as a whole. We know that it contains the secretions of all tissues and organs. Plasma and tissues being a closed system, any alteration in the tissues reacts on the plasma, and vice versa. During the course of life, this system undergoes

continuous changes. Some of these changes may be detected both by chemical analysis and by physiological reactions. The plasma or the serum of an aging animal has been found to increase its restraining effect on the growth of cell colonies. The ratio of the area of a colony living in serum, to that of an identical colony living in a saline solution and acting as a control, is called the growth index. The older the animal to which the serum belongs, the smaller is this index." "During the first days of life, blood serum does not inhibit the growth of cell colonies any more than does the control solution. At this moment the value of this index approaches unity. As the animal becomes older, its serum restrains cell multiplication more effectively. And the index decreases. During the last years of life, it is generally equal to zero." {Page 168.)

In 1921, a researcher (A. J. Lotka) looking for a job at the Rockefeller Institute visited Carrel's laboratory. "I saw a young lady making chicken hash in the most heartless but thoroughly scientific manner. I saw a little piece of chicken heart foolishly throbbing after all occasion for throbs had long ceased. I saw a thirteen year old dog rejuventated by the infusion of younger blood. It was hardly converted into a giddy young thing, but they told me there was still marked improvement even after twelve months." (S. E. Kingsland, *Modeling Nature*, Univ. of Chicago Press, 1995.)

Carrel discussed Lecomte du Nouy's equations for describing the regenerative activity of the body at a given age. (A 21 year-old person heals twice as quickly as a 40 year-old person.) The rate of healing and the growth index of plasma, according to Carrel, **"...correspond to successive states in the chemical composition of the humors. The proteins of blood serum become more abundant and their characters are modified. It is chiefly the fats which give to serum the property of acting upon certain cell types and of diminishing the rapidity of their multiplication. These fats increase in quantity and change in nature during life."** (Page 174.)

Here, I want to review some of the effects of fats that I have talked about elsewhere. Polezhaev's work in regeneration has suggested that the fatty residue left from degenerating cells stimulates the formation of new cells. Linoleic acid, like phorbol esters and estrogen, activates protein kinase C, and the cell growth system.

In looking at a tissue slide that was used to diagnose "ductal carcinoma in situ," I noticed that the structures resembled cross-sections of tubercles. In the breast ducts, fatty residues from milk secretions should be able to stimulate cell division. The fats formed by the tuberculosis bacillus stimulate the cellular reaction that produces the tubercle structure. Since a tuberculous breast grossly resembles a cancerous breast, it is important that the possible structural similarity of the two diseases, under the microscope, be considered. The bacteria can disappear from the cells in a tubercle, and the "defining" presence of giant cells in the tubercular lesion isn't invariable.)

It has been suggested that the tubercle develops and persists because the body's proteolytic enzymes are inhibited by the unsaturated fats. (Even older ideas of "fatty degeneration," going back to the very beginnings of biochemistry, were based on the fact that proteins are deposited from solution at an interface, such as that formed by a drop of oil, forming a sort of proteinaceous skin around fat droplets.) Whether the process is simply the result of inactivating proteolytic enzymes, or the result of a more specific disordering of cell control systems, it is a well established experimental fact that oils stimulate a kind of fibrous tumor, called the "oil granuloma." If the oil can't be digested and removed, the body reacts by forming a growth around it. Inside the cell, unsaturated fatty acids slow many cellular processes, including respiratory energy production and protein turnover, changes which parallel the changes occurring in aging.

About 30 years ago, Leonard Hayflick found that certain animal or human cells which can be grown in a dish would die out after about 50 divisions. He also found that cells from old individuals would stop dividing sooner when grown in tissue culture. He announced that this limited ability to divide sets the maximum limit of the lifespan. He has said that this is governed by the principle that entropy tends to increase. Another group found that the same kind of cell continued to divide nicely after 110 divisions, and didn't begin to

Reg 4

die out until they began to use the serum from a different calf. Their result resembled Carrel's findings, in which the fluid from younger organisms supported more vigorous growth in tissue culture, and clearly casts doubt on Hayflick's principle. But even without such contradictions of Hayflick's tissue culture results, Hayflick's claims couldn't really be taken seriously as anything but a theoretical model of what is happening to cells in an aging organism, because cells that are removed from their complex environment in the organism have been deprived of a rich and communicative framework.

The cells of the skin and bowel divide thousands of times in a normal lifetime, showing that there is a kind of arrogant silliness in the claim that "human cells have a strictly limited capacity to divide." (I call this "disproof by dandruff.")

Pieces of skin or mammary gland, removed from old rats and transplanted into young rats, remained healthy through the lifetimes of ten animals in series. When young animals have been surgically attached to old animals ("parabiosis"), the pair has lived out the life-span of the younger animal, allowing the older one to reach an abnormally advanced age. In some studies, beneficial changes have been seen in the old individual, and some harmful effects appeared in the young animal. I have described these experiments previously.

Selye's experiment, besides showing the importance of fluid renewal in cell aging, also showed one of the ways in which cells respond to structure. Cells build structures, and then they respond to them. They "know" where they are in a given structure. Cells produce materials--some of them soluble, others insoluble--that produce a characteristic local environment. In plants, the cellulose scaffolding between cells, and other extracellular matrix materials, serve as part of the information that guides the functioning of cells,[1] so that removal of the cellulose allows the cell to stop a specialized function, and begin to grow and take on new functions, even in some cases producing a complete new organism. In a wound in an animal's skin, cell division is stimulated to heal the wound. I think it is the doctrine of the germ line/somatic distinction that has prevented more vigorous research in the origin of teratomas, growths of radically different tissue types (hair, teeth, bones, fingernails, mammary tissue, e.g.) in an inappropriate location--often the ovary, but sometimes in the bladder, tongue, rectum or other location. These have been explained as "embryonic rests," or undeveloped Siamese twins, as a way to avoid the idea that somatic cells have the capacity to revert to totipotency. Their occurrence is strongly reminiscent of the situation in plants, in which an injured (isolated) somatic cell becomes "totipotent," resembling a germ cell or embryonic cell.

If cells have systems that regulate their functions, and known substances distrupt those functions, the endogenous regulatory material must have some of the properties of the disruptive material. For example, digitalis and ouabain are plant steroid-derivatives that are poisonous to animal cells--especially the heart cells--by acting at a "site" which is normally regulated by substances such as DHEA and progesterone.

For plants, cholesterol is a hormone, while it is only a precursor for hormones in animals. If plants ate animals, they might eventually accumulate enough cholesterol to disrupt the processes normally regulated by their very small amounts of cholesterol.

The fact that opium from poppies, and similar substances found in other plants, have a powerful effect on animals, and can be found associated with certain sites in their cells, led to the belief that these were regulatory sites, that might normally be controlled by very small amounts of materials produced in the animals' tissues, for regulatory purposes. This led to the discovery of the endorphins, the peptide molecules that have morphine-like effects.

Valium (or the traditional valerian root extract) was found to be associated ~~with a certain~~ "receptor site," which is now known as the "benzodiazepine receptor." A peptide called "endozepine" is one of the natural regulators of that control system, but it is also influenced by GABA (gamma amino butyric acid), progesterone, pregnenolone, and other materials. Butyric acid itself might affect this system.

Marihuana acts on cells by acting at a site that is called the "cannabinoid receptor," because the

Recepteur zodiazepine = valium, valerian Root, [enzodiazepine Regulariser le syst de recepteur zodiazepine et enzodiazepine est influencé par GABA, Proges, [illegible]

body's natural regulator acting on that site isn't yet known.

The unsaturated fatty acids, linolenic acid and linoleic acid, produced by plants, interfere with intercellular communication,[2] as well as intracellular regulatory sites. (PKC, osmotic balance[3], respiration.) The body's natural regulatory materials are probably similar in structure, but produced in controlled amounts and locations.

The Mead acids are unsaturated fatty acids produced in small quantities by the body when the diet doesn't contain an overwhelming amount of the plant-derived fatty acids. Wherever the plant fats act, we can expect to find a process that is regulated by the Mead acids, though not necessarily in the same way or with the same result. Even if the materials had the same effect on the control system, the increasing accumulation of an active material will tend to make control impossible, acting as a constant signal to activate the system. (Therefore, even an exaggerated accumulation of the natural transmitter substance would be disruptive if it were released in an uncontrolled way. The regulatory substance ideally would not be stored in excess, or it would be released in a controlled way. The Mead acids seem to meet these criteria.) [The position of the certain type of fatty acid on glycerol, for example, is regulated by specific enzymes.]

A naturally occurring combination of a fatty acid with ethanolamine, called anandamide, activates the "marihuana receptor" of cells. It prevents some types of cell activation. The Mead acid ethanolamide, like the arachidonic acid form, can be enzymatically formed in various human tissues, such as the hippocampus, but the two substances have slightly different effects. Marihuana's anticonvulsant properties might be more effectively represented by the Mead acid derivative. The anti-excitatory effect might also be effective in preventing the loss of cells in the hippocampus, hypothalamus, and other brain regions, which (building on Olney's work 25 years ago) is increasingly understood to result from excitotoxicity.

The architecture of tissues interacts with the cytoskeleton and the nuclear scaffolding to define the possibilities and opportunities that are available to the cell and to the organism.

The organization of life is maintained by the energy it uses, and the use of energy requires a specific organization. There are processes in cells that regulate the interactions of growth, division and other functions, but these processes are responsive to the cells' environment--they aren't just "emitted by" or "unrolled from" the cells' repertoire of abilities.

The cell's structure has sensitive "leverage" points that serve for purposes of "perception" or "signalling." When organization fails, it is just reasonable to consider whether extraneous conditions or "signals" have intervened. If it were in life's nature to become disorganized, it is hard to imagine that it would persist and thrive.

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Ray Peat's Newsletter

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Optimizing respiration

In a given situation, people who eat more are healthier and live longer than those who eat less--their bodies burn calories vigorously. In one study, fat people were found to be able to maintain their weight on only 700 calories per day, about a third of a normal calorie intake. In animal studies, too, the fast-metabolizers live longer than the animals that don't burn calories so fast. When animals are fed a calorie-restricted diet, and live longer than their *ad lib* fed relatives, people like to say that their "metabolic rate is depressed," but that isn't true: the under-fed animals are *smaller* than the *ad lib* eaters, but **each gram of their tissue burns energy at a higher rate.**

The biological value of the antioxidants is that they allow oxygen to be used productively, rather than destructively. When something interferes with the normal, productive use of oxygen, there is a great increase in the destructive forms of oxidation, such as lipid peroxidation, and the antioxidative reserves become crucial. That is, decreased respiration of the productive sort tends to increase the destructive use of oxygen.

Respiration in the ordinary sense is breathing, the exchange of gases between the animal and its environment.

Tissue respiration refers to the absorption of oxygen from the blood by cells, or, more exactly, to the exchange of gases between cells and their environment. Plants and other organisms respire in ways that are biochemically very similar to our tissue respiration.

Not all the oxygen we consume is put to good use, and we sometimes produce exhalations of gases other than carbon dioxide and water vapor.

Optimizing respiration means increasing the uses of oxygen that provide energy and increase functional capacity, while decreasing the forms of oxidation that impair functioning and decrease the production of useful energy.

In general, things which are associated with energy-producing respiration (such as thyroid hormone, carbon dioxide, coconut oil) also have roles as "antioxidants."

In 1895 Magnus-Levy demonstrated that hypothyroid people have abnormally low heat production, and that their heat production could be brought up to normal by giving them thyroid substance. In 1926, Otto Warburg showed that the respiratory enzyme, containing the heme group, is inhibited by carbon monoxide, which binds to that enzyme, as it does to hemoglobin. Warburg also showed that visible light restores the activity of the respiratory enzyme by dissociating it from the carbon monoxide. Beginning in the 1930s, many substances were found that blocked respiration and

Under stressful conditions, people may exhale measurable amounts of pentane, ethane, isoprene, carbon monoxide, and other substances with potential toxicity.

In hyperventilation, so much carbon dioxide is lost in the breath that our tissue respiration is impaired, creating a partial "tissue suffocation."

If cells consume oxygen without producing carbon dioxide generously, a situation analogous to hyperventilation/tissue suffocation exists.

Oxygen deprivation is one of the signals that stimulates the production of new red blood cells, and this involves the production of porphyrin, heme, and hemoglobin.

The elimination of heme by oxidation produces carbon monoxide, which can block the respiratory production of energy.

The heme group (of hemoglobin and the respiratory enzymes, for example) is the iron-binding oily molecule that interacts with oxygen, and it is called a porphyrin. There is a long history of investigating the interactions of porphyrin metabolism with estrogen (L. C. Strong, "Sex differences in pigment content of Harderian glands of mice," *Proc. Soc. Exp. Biol. Med. 50,* 123-125, 1942), with cancer (e.g., F. H. J. Figge, *et al., Cancer Res. 2,* 335-342, 1942), with diet, and with excess iron. Estrogens are known to cause porphyria (R. D. Levere, *Blood 28,* 569-572, 1966), and to exacerbate the symptoms and biochemical disturbances in people with subclinical porphyria. Sometimes symptoms occur premenstrually, during the time of increased estrogen production--the term "ovulocyclic porphyria" has been in use for a long time. Puberty therefore increases the susceptibility to symptomatic episodes. Jaundice in pregnancy and in oral contraceptive users is probably a closely related phenomenon. (H. F. von Oldershausen, *Deutsch. Med.J. 19,* 394-403, May 15, 1968.)

Porphyrin synthesis begins at an important cross-over point of protein and carbohydrate metabolism. Succinyl CoA and amino levulinic acid can enter the Krebs cycle or the porphyrin pathway. Protein catabolism feeds into these pathways. Increased protein catabolism or blockage of oxidative consumption of Krebs cycle fuel--for example by poisoning--makes these precursors available to enter the porphyrin pathway. Stress-induced oxidation of heme can eliminate feedback control, but the *specific* outcome can be modified in many ways.

Low blood sugar, most often caused by hypothyroidism, and diabetes--which involves poor absorption of sugar by cells--both tend to lower the respiratory quotient, the amount of carbon dioxide produced in relation to the amount of oxygen used. High carbohydrate diets, sometimes with insulin, have been used to treat porphyria (Perlroth, et al., Waxman, et al.). The use of carbon dioxide inhalation in psychiatry has many metabolic justifications, one of which might be the importance of carbon dioxide in glucose regeneration. It is also essential for detoxifying ammonia. Whenever a symptom is relieved by glucose, I think we should suspect that thyroid and carbon dioxide might be deficient.

Many serious long-range consequences of excess heme/porphyrin production and metabolism are currently being investigated, suggesting that the criterion of "twice the upper limit of normal" excretion that was recently proposed by a government agency, for recognizing that a problem exists, could allow far more serious problems to develop over time, that on the surface might seem unrelated to porphyria. I consider any porphyrin excess to be a serious indicator of physiological stress. **The ramifications of disturbed heme metabolism, resulting from exogenous factors, are far-reaching. For example, G. Y. Kennedy, at the Cancer Research Laboratory, University of Sheffield, observed that a porphyrin shortened the time required to induce tumors, and porphyrin derivatives have been proposed to be "cancer hormones."** The carbon monoxide produced in the breakdown of heme inhibits many enzymes. The consequences of slight excesses in porphyrin metabolism just haven't been investigated, because of the genetic dogmatism that denies that the person's environment could be at fault.

The synthesis of heme/porphyrin, and the production of red blood cells, are stimulated by a lack of oxygen, or by toxins such as arsenic and iron, which cause oxidative stress. Emphysema, high elevation, sluggish circulation, and nocturnal breathing problems can cause enough oxygen deficiency to stimulate the formation of new red blood cells. Newborn babies often have polycythemia, as a result of limited prenatal oxygen supply. At a certain point, the continued production of red blood cells can make the blood so viscous that this viscosity impairs circulation through capillaries, and creates a vicious circle, stimulating the formation of more red blood cells. Men are more likely than women to have polycythemia rubra vera, possibly because testosterone is anabolic to the bone marrow, and estrogen tends to slow blood cell formation (females of all species are relatively "anemic," compared to males, partly because their blood is more dilute), but I think the greater ability of men's marrow to respond proliferatively to hypoxia is influenced by many factors, including

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increased mucopolysaccharides in the skin (O. Braun-Falco, *Derm. Wschr. 136,* 1085, 1957). This is reminiscent of hypothyroid myxedema; it has been suggested that mucopolysaccharides can act as a matrix for calcification (W, C. Johnson, et al., *J. Invest.Derm. 43,* 453, 1964). Estrogen stimulates the formation of collagen (Loeb, et al.), and increases its age-like properties, and progesterone opposes some of these pro-aging effects on connective tissues. Mere lack of oxygen stimulates collagen formation (Chvapil, et al.), and the opposing effects of estrogen and progesterone on tissue oxygenation can account for many of the tissue changes they produce.

Oxygen deprivation causes tissues to retain calcium (and iron), as does estrogen in many cases, being similar to aging in promoting cellular uptake of calcium. Since the porphyrins strongly bind metals, it has been suggested that they may have a role in mediating the deposition of metals in stressed tissues. Paroxysmal vasospasm occurs in about 90% of scleroderma patients, and estrogen and adrenalin are known to synergize in producing vascular spasm; **hypothyroidism normally involves elevations of both estrogen and adrenalin.**

The porphyrins break down into bilirubin, which also poisons mitochondrial respiration (Zetterstrom and Ernster).

I have known women who developed scleroderma after beginning the use of estrogen, and who were reluctant to stop, because they had been told that estrogen would protect them from osteoporosis and heart disease. Men who have had a diagnosis of scleroderma have told me that with the use of thyroid and magnesium supplements, epsom salts baths, and topical progesterone and vitamin E, their symptoms regressed. I suspect that carbon dioxide produced in mitochondria is the main factor in removing calcium from them.

Polymyositis sometimes leads to calcification, and **this would be expected if the problem is related to mitochondrial respiration, as is now generally thought to be the case;** thyroid and magnesium are often the factors needed to normalize mitochondria and prevent calcification. In general, fatigued cells take up calcium and lose magnesium.

Many people get minor bony excrescences (bone spurs, osteophytes, exostoses, hyperostoses) during puberty or menopause, or at other times of hormone imbalance, which often disappear spontaneously. This would have very little to do with the severe oxygen deficiency states in which collagen synthesis is overstimulated and general calcification occurs. Growth hormone and prolactin imbalances have been suspected to have a role in some of these growths, and cortisol--which is is active in several aspects of bone metabolism--is probably involved (all of these hormones are elevated by estrogen, and hypothyroidism is often responsible.) Progesterone, thyroid, bromocriptine, and other things are available to normalize the pituitary, when that is malfunctioning. The bone spurs that develop during times of fluctuating thyroid function, might also be promoted by rapid changes in calcium and carbon dioxide levels. (The description of bone mineral as "apatite" leads many people to forget its carbonate content.)

In general, lactic acid in the blood can be taken as a sign of defective respiration, since the breakdown of glucose to lactic acid increases to make up for deficient oxidative energy production. Normal aging seems to involve a tendency toward excess lactic acid production, and age-pigment is known to activate the process. Eliminating respiratory toxins (such as unsaturated oils, estrogenic and antithyroid substances, lead, and excess iron) is the most obvious first step to take when there is excess lactic acid formation. Carbon dioxide supplements have been shown experimentally to reduce residual lactate production. Many people experience exhilaration when they go to very high altitudes, and it is known that people generally burn calories faster at high altitude. **It has been found that, during intense exercise (which always produces a lactic acid accumulation in the blood), a lower peak accumulation of lactate occurs at high altitude, and this seems to be caused by a reduction in the rate of glycolysis, or glucose consumption.** (B.Grassi, et al.) Since there is less oxygen at high elevation, and since oxygen is used to consume lactic acid, this effect is the opposite of what many people expected. In some sense, respiration becomes more efficient at high altitude. Youth and increased

times supported the process by helping to stabilize the high energy metabolism of the brain, and even by stabilizing the "energized" state of water that supports brain efficiency. Roman Schmitt has proposed that, 66 million years ago when dinosaurs became extinct and mammals began their rapid evolution, "at that time hydrothermal venting went wild," releasing huge volumes of carbon dioxide and other substances into the atmosphere.

Antarctic ice cores show there were large increases in atmospheric carbon dioxide in relatively recent times: 10,200, 11,600, and 12,900 years ago, and two broad peaks in carbon dioxide release occurred just 4,200 and 7,700 years ago. (Figge and White.) Local or regional increases in carbon dioxide from volcanism could have more continuous effects on brain development.

In times of lower atmospheric carbon dioxide, our Krebs cycle still produces it internally, and the rapid development of the brain during gestation takes advantage of the high concentration of carbon dioxide in the uterus. (These ideas make me doubt the safety of the rapid breathing encouraged by some obstetricians.)

A weakened ability to oxidatively produce energy can lead to the maladaptive over-production of collagen, porphyrins, red blood cells, and other tissues and substances, which in turn can lead to many adaptive and maladaptive changes. I think skin and mucous membranes provide a good illustration of the way respiratory potential influences structure: Estrogen-increased keratinization is opposed by vitamin A, which increases the proportion of active, differentiated cells.

Changes that begin as functional adaptive processes can lead to structural and anatomical changes that contribute to functional derangements. *If we look at small anatomical structures such as capillaries, we can see that our anatomy is in flux, adjusting structures to meet changing needs.* After every experience of stress or trauma, we have to reconstitute ourselves. When this rebuilding lags, defects accumulate. Rosacea, diabetes, and systemic lupus erythematosa are examples of conditions that progress from functional to anatomical abnormalities.

Our organization is built on the basis of interacting structures and functions. Adequate respiration depends on adequate structures, and adequate structures require adequate respiration.

Anatomical structures, tubes, spheres, and sheets of cells, create gradients and fields as materials move through them, in relation to which cells organize themselves. Changes in simple electrical fields can cause radical changes in the behavior of cells. Changes in respiration cause many changes in chemical and electrical gradients, and the intensity of respiration is known to be a central factor in the development and preservation of biological form. Child's work on the developmental importance of metabolic gradients (summed up in *Patterns and Problems of Development,* 1941) has been confirmed and refined, despite the immense effort that has been spent on genetic mystification of the processes that create and maintain form.

The quality of the developing brain of the fetus, the deterioration of the aging immune system, and hundreds of other processes are governed by the quality of respiration.

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J Surg Res 1984 Jul;37(1):63-68 Evidence for aerobic glycolysis in lambda-carrageenan-wounded skeletal muscle. Caldwell MD, Shearer J, Morris A, Mastrofrancesco B, Henry W, Albina JE "Classically, increased lactate production in wounded tissue is ascribed to anaerobic glycolysis although its oxygen consumption has been found to be similar to normal tissue. This apparent inconsistency was studied in a standardized isolated perfused wound model. Male Sprague-Dawley rats were wounded (group W) with intramuscular injections of lambda-carrageenan and fed ad lib.; not wounded and pair fed to the decreased food intake of the wounded animals (group PFC); or not wounded and fed ad lib. (group ALC). After 5 days, the hindlimbs of animals from each group were either perfused using a standard perfusate with added [U-14C]glucose or [1-14C]pyruvate or assayed for the tissue content of lactate and pyruvate. In addition, the effect of a 30% hemorrhage on the tissue lactate and pyruvate concentration was examined. **Wounding increased glucose uptake and lactate production by 100 and 96%, respectively, above that seen in ALC animals.** Oxygen consumption was unchanged by wounding (5.74, 5.14, and 5.83 mumole/min/100 g in W, PFC, and ALC, respectively). Glucose and pyruvate oxidation were also unaltered among the groups. Hemorrhage resulted in a comparable increase in lactate and pyruvate in tissue from wounded and pair-fed control animals (above those concentrations found in tissue harvested without preexisting hemorrhage). As a consequence, the same relationship in L/P ratio was maintained after hemorrhage. Taken together, these results confirm the **presence of aerobic glycolysis in wounded tissue** (unchanged oxygen consumption, glucose, and pyruvate oxidation). In addition, pyruvate dehydrogenase activity in the wound was apparently the same as that found in muscle from pair-fed control animals."

Food Chem Toxicol 1984 Aug;22(8):615-621 Effect of orally administered food-grade carrageenans on antibody-mediated and cell-mediated immunity in the inbred rat. Nicklin S, Miller K "Experiments were performed to investigate the immunological consequences associated with the persorption of poorly degradable carregeenans from the diet. Using an inbred strain of rat it was demonstrated histochemically, by the carrageenan-specific Alcian blue staining technique, that **small quantities of food-grade carrageenans given at 0.5% in drinking-water for 90 days could penetrate the intestinal barrier of adult animals. This apparently occurred via an intact mucosa in the absence of inflammatory or pathological lesions. The carrageenan was demonstrated in macrophage-like cells present within the villi and lamina propria of the small intestine.** The oral administration of kappa, lambda or food-grade carrageenans did not affect local (biliary) or antibody responses to gut commensal microorganisms, or to orally-administered sheep erythrocytes. However, when sheep red blood cells were administered parenterally the ensuing anti-sheep red blood cell haemagglutinating antibody response was temporarily suppressed in carrageenan-fed rats. lambda-Carrageenan and iota-carrageenan both significantly (P less than or equal to 0.01 and P less than or equal to 0.05, respectively) reduced the mid-phase (14-28 days) haemagglutinin response; kappa-carrageenan (L100) was less effective but caused significant depression at day 21 (P less than or equal to 0.01). Individual responses were, however, within the control range 35 days after sheep erythrocyte administration, thus indicating the temporary nature of this effect. Although carrageenan administration depressed the anti-sheep erythrocyte antibody response, it did not affect T-cell immune competence as measured by the popliteal lymph node assay for graft-versus-host reactivity."

J Nutr 1986 Feb;116(2):223-232 Effects of certain dietary fibers on apparent permeability of the rat intestine. Shiau SY, Chang GW "Apparent intestinal permeability was determined indirectly by orally administering a poorly absorbed dye, phenol red, to rats and measuring its recovery in feces and in urine. Increased apparent permeability was recognized by increased dye recovery in urine and by an increased ratio of urinary to fecal dye recovery. Guar gum, pectin, carrageenan type I (80% kappa, 20% lambda), carrageenan type II (iota) and cellulose were each fed at levels of 5 and 15% (wt/wt) of the diet for 31 d to male Fischer 344 rats. The average initial weight of rats was 230 g. Rats fed 15% guar gum gained significantly less weight than most of the other rats (P less than 0.05). Phenol red recovery was measured at 2 and 4 wk after the beginning of the experiment. **At 2 wk urinary recoveries of phenol red were high in rats fed fiber-free and carrageenan type II diets, indicating increased apparent permeability.** By 4 wk, adaptation had apparently taken place." "These data are consistent with the hypothesis that intestinal permeability to foreign substances may be altered considerably by diet."

Pathologe 1993 Sep;14(5):247-252 [Persorption of microparticles].[Article in German] Volkheimer G "Solid, hard microparticles, such as starch granules, pollen, cellulose particles, fibres and crystals, whose diameters are well into the micrometre range, are incorporated regularly and in considerable numbers from the digestive tract. Motor factors play an important part in the paracellular penetration of the epithelial cell layer. From the subepithelial region the microparticles are transported away via lymph and blood vessels. They can be detected in body fluids using simple methods: only a few minutes after oral administration they can be found in the peripheral blood-stream. **We observed their passage into urine, bile, cerebrospinal fluid, the alveolar lumen, the peritoneal cavity, breast milk, and transplacentally into the fetal blood-stream. Since persorbed microparticles can embolise small vessels, this touches on microangiological problems, especially in the region of the CNS.** The long-term deposit of embolising

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Progesterone, thyroid, cancer

In the first half of the twentieth century, Otto Warburg and Albert Szent-Gyorgyi proposed that proliferation is the natural "primordial" tendency of all cells, including those in complex multicellular organisms, in which many cells remain in a quiescent, non-proliferating state for years. Their orientation was similar to that of Johanes Muller, who in 1840 argued that cancer might originate at the level of tissues, rather than in the nature of the individual cells making up the tissue.

Both Warburg and Szent-Gyorgyi showed that oxidative metabolism is crucial in maintaining the relative quiescence that makes it possible for multicellular organisms to exist and to preserve their organization. In these organisms, the individual cells are embedded in a glue-like matrix, in the case of animals, or in a woody scaffolding, in the case of plants; the oxygen and nutrients needed by the cells diffuse through the matrix, so its condition is crucial for the cells' functions. The extracellular matrix, and the materials that pass through it, constitute the "field" within which cells develop and function.

Early researchers understood that the connective tissue matrix changes progressively in aging, which is evident in the fact that the meat of old animals is tougher than that of young animals. Leo Loeb, studying the effects of estrogen on the uterus, showed that it increased the formation of collagen, causing cells to be separated from their blood supply by a thickened barrier of water and collagen.

Estrogen, by altering the cell matrix, alters the developmental field itself. Simply by creating a thickened barrier, it makes it difficult for cells to maintain their proper place in the organism, and some of them, in the energy-deprived state, revert to the primordial proliferative state.

Thyroid hormone, the regulator of oxidative metabolism, is the basic hormone making possible the respiration which generates and sustains the multicellular state.

The simple idea of antagonism between hormones, for example between catabolic and anabolic steroids, or between progesterone and estrogen, is firmly based on experiments, but there is an attitude in medical endocrinology, based on the names of the substances, that insists on a "synergy" between estrogen ("the hormone of estrus, creating a readiness to copulate") and progesterone ("the hormone of pregnancy"). Sequential, coordinated action isn't the same as synergy. Hunger can lead to satiety, but no one denies that these are contrasting conditions. Hundreds of biological actions created by estrogen are reversed by progesterone, and vice versa.

Shock, capillary leakage, excessive clotting of the blood, epilepsy, goiter, hyperactivity, and countless other biological problems are created by an excess of estrogen, and normalized by progesterone. The problem of cancerization by estrogen, and its opposition by progesterone, was clearly defined by Alejandro Lipschutz more than fifty years ago, but a series of deliberate actions by the drug industry, and its "regulatory agencies," has prevented a rational and coherent approach to the use of hormones in preventing and curing cancer.

For over fifty years, estrogen has been widely promoted for the prevention and treatment of various cancers, and throughout the 20th century agents of the drug industry claimed that it was not carcinogenic, and prevented the US government from classifying it as such. During the same period, and for many of the same commercial reasons, natural progesterone has occasionally been claimed either to cause cancer, or to be ineffective in its treatment. While billions of dollars were spent in "cancer research," the useful basic knowledge about the prevention and cure of cancer was ignored. Not just ignored, but suppressed: Medical journals of all sorts have simply declined to publish favorable research on

progesterone, and medical conferences on female endocrinology that claim to be open to all views are not open to favorable reports on progesterone.

Some researchers have observed that only about one percent of medical research is scientifically sound, but that view ignores the fact that the "valid one percent" is certainly going to be misinterpreted, unless the reader understands that the medical journals are intensely subjective and biased in what they choose to publish, and that they exclude the research that would provide the essential contexts for evaluating the things that ***are*** published. To find an adequate context in which to interpret current research, we have to go back at least fifty years, to a time when the science journals were relatively independent.

The idea of "genetic determination," which I have written about many times, has been useful to the drug industry. If moderate amounts of estrogen didn't cause mutations of certain genes that were thought to distinguish normal cells from cancer cells, then how could it be carcinogenic? And if cancer cells are "genetically committed," then only lethal cytotoxic methods could be considered as therapies.

The history of estrogen and progesterone research offers an alternative view of cancer, and of physiology itself. In the 1940s, Hans Selye demonstrated that progesterone produced very deep anesthesia, and that its actions were essentially instanteous. Estrogen's characteristic actions, too (such as the uptake of water by tissues, and nervous excitation) were so rapid that it was clear that the effects were produced without the activation of special "genes." But these quick actions were generally ignored, because their existence wasn't compatible with the doctrine of genetic determination.

Estrogen acts at many different levels, modifying the state of water, of proteins and fats, of the immune, circulatory, and nervous systems. It isn't just a "carcinogen," or just a "female hormone." Many substances, processes, or conditions (cholera toxin, x-rays, oxygen deprivation) imitate many of estrogen's effects.

Energy generates order, and maintains it. Destruction of order degrades the ability of cells to produce energy.

Progesterone (and related substances), too, act on many levels of organization at the same time. The interactions of proteins and water are changed immediately, with circulatory and nervous and bioelectrical responses coinciding with changes of cells' functions, including changes in the proteins of the "receptor systems." The functional changes that can be seen in the first minutes of progesterone's actions lead to metabolic changes and then to more basic structural changes.

Stabilization and activation of mitochondria by progesterone, and a shift away from glycolysis (Joe and Ramirez, 2001: GAPDH inhibition), are exactly the opposite of estrogen's toxic effects on the mitochondria (by increasing NO, for example), and activation of glycolysis.

On the molecular level, progesterone and estrogen have different structural effects, that account for their globally opposite regulatory effects. Their systematically different effects on energy production lead to global differences in the regulation of cytokines, neurotransmitters, hormones, and cellular organelles, which contribute to macroscopic shifts in the distribution of substances throughout the organism, including water, fats, and the materials such as collagen and glycoproteins that make up the extracellular matrix.

If progesterone is to be named "the hormone of gestation," then estrogen might be called "the hormone of miscarriage."

The characteristic metabolic end-product of progesterone-dominated metabolism is carbon dioxide. During gestation, the fetus is exposed to large amounts of progesterone and carbon dioxide. The very high concentration of progesterone during gestation keeps tissues from retaining excess estrogen, even when estrogen is present in the blood stream. The very high concentration of carbon dioxide has many protective effects,

Every tumor is a biologically unique substance, but it is biologically compatible with its host. This is analogous to the tissue compatibility of twins which share a single placenta, even though they may be genetically different fraternal twins.

including protection against the formation of lactic acid.

The characteristic metabolic end-product of estrogen-dominated metabolism is lactic acid. Increasing lactic acid displaces carbon dioxide.

Carbon dioxide combines spontaneously with amine groups, as in the lysine residues of proteins, and this influences the interactions of the proteins with other substances, for example, inhibiting glycation of proteins; protein glycation occurs during stress and aging, and degrades the functions of proteins and cells and systems. These changes are believed to contribute to the hardening of connective tissues with aging.

The fibrosis of aging is associated with a generalized state of inflammation, producing catabolism and atrophy of most systems, with isolated regions escaping the general cachexia, and regenerating their cells and tissues in disorganized ways, producing many abnormalities that could be diagnosed as "precancerous," a few of which develop into tumors.

A.V. Everitt's book on the pituitary and aging mentions some studies that relate to progesterone and aging. Uterine collagen aging, which increases under the influence of estrogen, is lowest in the old rodents that have been bred the most often, and this is probably partly the result of progesterone's action on collagenase and fibroblasts, as well as its ability to displace estrogen from the tissues. Leo Loeb showed that excess estrogen and aging both produced similar increases in collagen. Alejandro Lipschutz found that chronic estrogen treatment produced fibrosis of practically all tissues, and that cancer later developed in those fibrotic tissues. Then he tested various steroids, and found that progesterone had the strongest antifibromatogenic action, and that pregnenolone was next in effectiveness. (Brief intermittent exposures to estrogen didn't produce the harmful effects, and now it's known that progesterone decreases the tissues' retention of estrogen.) Lipschutz' 1950 book on steroid hormones and tumors summarizes his work.

Contemporaries of Loeb and Lipschutz, Joseph Needham, C.H. Waddington and J.W. Orr, argued that cancer evolves through a series of developments in the tissues, rather than in single cells.

A few years later, Hans Selye showed that the partial isolation of tissue itself (for example, growing inside a small glass tube implanted in a rat) caused a tremendous acceleration of the aging process in the isolated cells and matrix. An impermeable sheet of plastic implanted in an animal tends to cause a cancer to develop, if it is folded to form a concavity. The thickened connective tissue matrix that develops with aging, irritation, and stress creates innumerable areas in which cells are similarly cut off from full contact with their normal environment.

Estrogen treatment at menopause produces alkalosis and hyperventilation. Alkalosis stimulates peroxidation and various other harmful stress-products. Prenatally, if estrogen excess doesn't kill the fetus, it retards its brain growth, because many of its metabolic actions are powerfully antigestational--actions that are used medically in the contraceptive pills and abortion pills.

All cancer cells produce lactate even in the presence of oxygen, and this increases their intracellular alkalinity, promoting swelling, calcium uptake, and proliferation. Continued exposure to lactic acid increases collagen formation and fibrosis.

I think of high altitude as analogous to the protected gestational state. (Both progesterone and carbon dioxide are increased in people adapted to high altitude.) Respiratory acidosis, meaning the retention of carbon dioxide, is very protective, and is an outstanding feature of life in the uterus. Even at the time that an embryo is implanting in the uterus, adequate carbon dioxide is crucial. Many of the mysteries of embryology and developmental biology have been explained by the presence of a high level of carbon dioxide during gestation. For example, an injury to the fetus heals without scarring, that is, with complete regeneration instead of the formation of a sort of collagenous plug. Over the last fifty years, several people have discovered that simply enclosing a wound (for example an amputated finger tip) in an air-tight compartment allows remarkably complete regeneration, even in adults, who

supposedly have lost the power of regeneration. (Exposure of tissues to air causes them to lose carbon dioxide.)

High altitude sickness is now treated with acetazolamide (which causes carbon dioxide retention, and respiratory acidosis), or with direct inhalation of carbon dioxide. Sleep apnea, which has been treated for many years with progesterone, is now being treated with acetazolamide, in recognition that it is caused by alkalosis. Both progesterone and acetazolamide increase the carbon dioxide content of the tissues, by decreasing sensitivity to carbon dioxide, yet they both stimulate respiration by increasing sensitivity to oxygen deprivation. (Wagenaar, et al., 2000.) Drugs similar to acetazolamide, sulfonamides that inhibit carbonic anhydrase, have recently been discovered to stop the growth of a wide variety of tumors.

Carbon dioxide, progesterone, and the carbonic anhydrase inhibitors stabilize and protect cells in very general ways. For example, they all inhibit epileptic seizures. All of them are involved in regulating calcium, preventing bone loss and hypercalcemia. In cancer, hypercalcemia is very common, and it is important to be able to correct it, because uncontrolled calcium is profoundly dangerous. (In "Homeostasis" and other newsletters I have written about the regulation of calcium.)

Increased intracellular calcium is excitatory, and interferes with mitochondrial energy production. Prolonged oxygen deprivation increases intracellular calcium (Smith, et al., 2001). When a cancer cell interacts with other cells, it can disturb their calcium regulation, and this can cause the cell to break its contacts with other cells (Tsuji, et al., 2002), and increased intracellular calcium can cause a cell to reorganize its intracellular structure, and to be transformed into spontaneously proliferating cells (Furst, et al., 2002). The intracellular architecture which is depolymerized by calcium excitation forms a link between the extracellular matrix and the regulation of genes in the nucleus. Generally, things (estrogen, prolactin, alkalinity, swelling, cadmium, iron) that increase intracellular calcium increase cellular proliferation. Drugs that decrease intracellular calcium are increasingly being seen to stop the proliferation of cancer cells.

Increased intracellular calcium also increases the formation of collagen, and drugs that decrease intracellular calcium decrease collagen secretion.

If cancer consists of a spontaneous process of healing and regeneration that goes wrong because of changes in its environment, because it has lost contact with its "formative field," then the only reasonable approach to the prevention and treatment of cancer is to restore that formative field. The conditions of gestation, for mammals, constitute a formative field in the highest degree that we know.

During gestation, after organs have differentiated, nerve cells extend their fibers from the brain to innervate muscles and other tissues. The special conditions of life in the uterus support this process, but something similar can happen during adult life, when damaged nerves regenerate. A major difference between injury to the fetus, and injury to an adult, is that the wound regenerates perfectly without a scar in the fetus, but in the adult, regeneration is often impaired, and a connective tissue scar replaces normally functioning tissue.

The intestinal nerves of stressed animals have been found to fragment; before the axons actually break, they form beads. (Beaded nerves are often seen in fresh tissue specimens that aren't treated by dehydration and embedding.) The surface tension of an axon has to be very low, for it to remain stable with such an extreme ratio of surface to volume: the diameter of an axon is similar to that of a bacterium. Ordinary water, with its high surface tension, breaks up into drops rather than forming a filament. If something increases the surface tension of a nerve, it tends to round up; the glial cells and Schwann cells that surround the axons of fast-acting nerves provide pregnenolone and progesterone to the axon, and the extreme lipophilicity of progesterone lowers the surface tension of cytoplasm. Progesterone powerfully improves nerve cell regeneration. During stress, cells run out of oxygen and produce lactic acid instead of carbon dioxide, and the lipophilic and acidic gas is replaced by the hydrophilic lactate.

Carbon dioxide protects nerves and muscles against excessive excitation. It inhibits lactic acid formation, and lipid peroxidation (measured in the blood) can be completely suppressed by a pCO2 of about 90 mm, which isn't high enough to produce acidosis.

Hospital respirators are normally set to hyperventilate patients, and the use of supplemental oxygen tends to make hyperventilation worse, making breathing and circulation more difficult. Carbogen, 95% oxygen with 5% carbon dioxide, is available, but is seldom used. Hyperbaric oxygen is both safer and more effective when carbon dioxide is added, but the amount of carbon dioxide needed varies with the pressure. More people would recover from brain and spinal cord injuries if physicians understood nerve and respiratory physiology.

One of the most commonly recognized features of estrogen excess is leakiness of the capillaries. Simple hyperventilation is enough to cause capillaries to leak, and this involves many related events, including decreased carbon dioxide, and increased release of serotonin. Edema, fibrosis, and inflammation (resulting from capillary leakage) contribute to a change in cellular energy production, and along with the actions of serotonin and other regulatory substances released during the alkalosis of stress, cells are stimulated to multiply.

The excitation of cells produced by a deficiency of carbon dioxide increases their need for energy. If their energy production is suppressed (as by estrogen, serotonin, and edema), they will either adapt or die.

In the isolation of a degenerating extracellular matrix, with a defective energy supply, some cells will react as though they are going to repair a wound or regenerate tissue, proliferating and degrading the damaged matrix, but instead of encountering healthy tissue, they sometimes encounter only more damaged tissue, and other cells in the simplified, proliferating state. Without finding the stable field of a healthy organism, they will continue to adapt and develop, but with reference to a field that has no function. Eventually, that kind of disoriented adaptation can produce a malignant tumor.

A 1951 Symposium on Steroids in Experimental and Clinical Practice (held in Cuernavaca), edited by Abraham White, has a chapter by Roy Hertz, et al, "Observations on the effect of progesterone on carcinoma of the cervix," that follows up on the antitumorigenic effects of progesterone discovered by Lipschutz, and the chapter includes some very interesting photographs of cervical tumors before and after treatment, and they reported that "In eleven of the 17 treated patients visible and palpable evidence of regressive alteration of the tumor mass could be demonstrated. This consisted of (a) distinct reduction in size of the visible portion of the cancer as well as reduction of the palpable extent of the mass, (b) reduction in vascularity and friability of the visible lesion with a clearly demonstrable epithelization of previously raw surfaces and (c) markedly increased pliability of the previously rigid and infiltrated parametria." *[That is, the bloody messes started healing, and the woody lumps began to feel like normal tissue.]* Despite the amazingly favorable results, they conclude "We do not consider the regressive changes observed to be sufficient to indicate the use of progesteone as a therapeutic agent in carcinoma of the cervix." This conclusion is especially interesting, considering that two pages later, Escher, et al., say that the highly ambiguous effects of estrogens on breast cancer "are of value to advanced-cancer groups." I think it's likely that the institutional sponsorship of the symposium influenced those conclusions.

Hertz, et al., gave the women 250 mg of progesterone in 5 ml of vegetable oil i.m., usually daily, for ten to 170 days. They didn't mention any side effects of sedation or anesthesia. Hans Selye found that large doses of progesterone caused profound anesthesia in rats, ***but this effect has never been reported in humans, because the pharmaceutical forms of progesterone don't permit adequate doses.*** Using progesterone dissolved in tocopherol (at 10% or 20% concentration), it takes only 100 mg to semi-anesthetize some people, and very profound anesthesia can be produced by larger doses. (In this form, a very large dose can kill a rat, though it stimulates the respiratory center at lower anesthetic doses.)

Progesterone is barely soluble in ordinary vegetable oils, and publications rarely mention that the formulations which contain 250 mg/ml also contain the "bacteriostat," benzyl alcohol, which is the actual solvent, but which is so soluble in water that the progesterone crystallizes immediately after intramuscular injection. (I have previously written about the history of medical progesterone, and the fraudulent claims and doctrines that have shaped its use.)

Although my observations show that progesterone is much more effective in treating many kinds of cancer than most of the published literature indicates, journal editors "know" otherwise. When I applied for the patent on the formulation of progesterone in vitamin E, the patent examiner told me that I must remove any mention of cancer if I wanted my application to be approved. The "evil mutant cell" theory of cancer, and the official description of progesterone as a "gestational hormone" or progestin, combine to create an attitude that doesn't want to think very long about progesterone's general regulatory functions in the organism.

Synthetic "progestins" have some of the properties of progesterone, and many studies have shown that they can be curative when used against several kinds of cancer. But the prevailing cancer culture has led to their use in combination with cytotoxic chemicals, and/or radiation, rather than with the factors that would really synergize with their "progestational" actions: The factors that would correct the formative, organismic field.

Since part of progesterone's therapeutic action is its ability to raise the concentration of carbon dioxide in the tissues, other techniques that increase carbon dioxide should be used at the same time. Thyroid's action is crucial for the production of carbon dioxide, and for the avoidance of lactic acidosis, adrenalin excess, and other processes that lower carbon dioxide concentration. (And, of course, thyroid is essential for the synthesis of progesterone, and for restraining the synthesis of estrogen, and accelerating its elimination from the body.)

Progesterone, thyroid, and carbon dioxide all protect against the cancer-promoting actions of calcium, and they do this by increasing respiratory energy, which favors intracellular magnesium over calcium. Adequate magnesium in the diet is extremely important. It is counterproductive to eat a calcium-deficient diet, since that tends to increase the intracellular calcium at the expense of calcium taken from the bones.

The immense power of the pharmaceutical industry, and its controlled government agencies, creates a situation in which the work of people like Lipschutz and Needham is written out of the culture. With the loss of a meaningful context, individuals with an authoritarian inclination will believe that science consists of comparing the latest therapeutic products or technologies with the earlier products or technologies. Some of the newer products and technologies will be sold as "alternative medicine," by a different branch of industry. But if the newer alternatives still conform to the view of cancer and life that was created to sell the old products, they can never make a real difference.

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Ray Peat's Newsletter

Progress might have been all right once, but it has gone on too long. Ogden Nash

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Pathological Science & General Electric: Threatening the paradigm

Everything in biology depends on the internal order of cells, and on the interactions of each cell with its surroundings. All of these orderly interactions involve contacts between biological molecules and water. The forces regulating interactions on that scale must be understood before life can be understood, but the nature of the forces at these interfaces has been controversial for 100 years.

In 1953, physicist Irving Langmuir gave a talk at the General Electric laboratory about what he called "pathological science." That talk is still resonating in the scientific culture, and it is used to reinforce attitudes similar to those held by Langmuir, i.e., the dominant scientific paradigm of the 20th century, and to justify certain institutions that regulate innovation.

For Langmuir, there was a clearly defined "scientific method," and he said some people were led away from the proper method by wishful thinking to interpret ambiguous results as confirmations of their hypothesis. He listed 6 symptoms of pathological science: 1) An effect produced by a barely detectable cause, and 2) the effect is barely detectable, or many measurements are needed because of the very low statistical significance of the results, 3) claims of great accuracy, 4) they involve fantastic theories contrary to experience, 5) criticisms are met by *ad hoc* excuses, and 6) the ratio of supporters to critics approaches 50%, then fades toward zero. He failed to mention these features in any research that supported his view of things, and called an idea pathological when people continued to work on it despite disapproval by the recognized experts. He didn't mention the Nobel prizes that were given for the worm theory of cancer or for treating psychological problems with lobotomies, and he didn't mention that there were organized campaigns against the publication of disapproved ideas.

The dominant view in biology, which is analogous to Langmuir's view in physics, is that all decisive cellular processes involve the direct mechanical contact of one molecule with another, the activation of a lock (an enzyme or receptor) by a key that has the right shape, or the adhesion of a molecule to another substance according to its chemical composition. An alternative view, now clearly supported by the evidence, is that there are forces that aren't merely between molecular surfaces, but rather that the local conditions at the surfaces of proteins and other molecules, and the properties of the solvent water, are modified by the surrounding conditions. It is this alternative view that is now making progress in understanding disease and health, regeneration and degeneration. But to judge the new work, it's important to know the nature of the opposition.

Thomas Edison, who was adept at publicizing himself as the inventor of ideas he had bought or stolen, founded General Electric. Attempting to eliminate Nikola Tesla's system of alternating current, since Edison was invested in direct current systems, Edison's GE tried to convince the public that direct current was safer, by using alternating current to electrocute an elephant, and by promoting its use in the electric chair. GE eventually gave up the direct current technology for electrifying cities, and they refined the electric light bulb and were fairly successful in controlling, practically monopolizing, that market, and in shortening the life of incandescent bulbs. Carbon filament bulbs made around 1900 often lasted decades; I had one that kept working until it was broken during a move in 1960. Light bulbs made in England 65 years ago, and in the Soviet

Union, and bulbs currently made in China, had a life expectancy five times as long as the bulbs made in the US since GE learned how to carefully control the rate at which the tungsten filament deteriorates.

Irving Langmuir was their leading light bulb scientist. In his 1932 Nobel lecture, he tediously argued that molecules of gas can form only one layer on a surface such as a filament. About 17 years earlier, Michael Polanyi had demonstrated that molecules can be adsorbed in multilayers, but his evidence was dismissed because, according to the understanding of industrial experts such as Langmuir, and the leading scientific authorities, Einstein, Nernst, and Haber, it was impossible. They were committed to an explanatory system that didn't allow events such as those Polanyi described.

Although Polanyi knew that his adsorption isotherm was more realistic than Langmuir's (he had demonstrated many cases that Langmuir's didn't describe correctly), and also easier to understand, he taught Langmuir's isotherm to his students, because he knew that they would be required to know it to pass their examinations. He knew he had risked his career by his earlier exposition of his ideas, and he was unwilling to endanger his students' careers by involving them in the controversy.

From 1920 to 1926, before the advent in 1927 of "quantum physics" (with its still-argued features of delocalized electrons, molecular orbitals, resonance, non-locality, incommensurability, indeterminism), Polanyi had turned his attention from the physics of adsorption to chemical structure, and his group was the first to show that cellulose was made up of long molecules, polymers, rather than of just associated clusters. That idea didn't catch on, so he turned to the behavior of crystals and metals. He found that crystals were much weaker than they should be, according to the strength of the bonds between their atoms, and showed that this was because of defects, and that during repeated stresses, they became weaker, as energy migrated through relatively long distances in the substance, to concentrate the defects. The idea of lattice defects was acceptable at that time, but long-range mobility of bond energy was no more acceptable then than it had been when J.C. Bose described metal fatigue, decades earlier.

Polanyi also showed that the strength and rigidity of a crystal were altered when the crystal was immersed in water. Again, such an influence of a surface on the over-all physical properties of a solid substance had no noticeable effect on the scientific culture, although his results were published in the major journals. To adjust one's interpretive system at that time to rationalize Polanyi's results would have required discarding the basic assumptions that were behind Einstein's explanation of the photoelectric effect, and maybe even his theory of Brownian motion. However, by 2011, fewer people have invested their personal development in those ideas of short-range electrical binding forces that prevailed early in the 20th century, and now, for example, the evidence of "delocalized holes in DNA" can be discussed more openly. Eventually, science textbooks may be rewritten to show a steady progression of understanding from Bose, though Polanyi, Perutz, Szent-Gyorgyi, Ling, and Damadian (inventor of the MRI, holder of the patents infringed by GE, non-winner of the Nobel prize).

In 1933 J.D. Bernal had proposed a structural model of water that contained a considerable amount of order (Bernal and Fowler, 1933) but by the 1950s the idea of spontaneous ordering in water was out of style, and he worked out a more random structure. Max Perutz, continuing the study of hemoglobin he had begun with Bernal, became concerned with long range forces acting through water: "The nature of the forces which keep particles parallel and equidistant across such great thicknesses of water is not yet clear." Normal wet crystals of methemoglobin contain regular layers of water 15 Angstroms thick. He suggested that a laminated structure of the water could plausibly explain his measurements. Comparing the protein crystal to montmorillonite particles, which incorporate several layers of water, each 3 Angstroms thick, each layer of water in the protein crystal would be 4 Angstroms thick, since swelling proceeds in discrete steps of that thickness. 52.4% of the volume of Perutz's normal, stable, wet protein crystals consisted of

liquid. Part of the water is a fixed monolayer, but the rest is apparently in the form of mobile, interactive, multilayers. By 1952, Perutz had decided that long range forces weren't involved in hemoglobin crystallization, but he didn't comment on the long range ordering of clays, tobacco mosaic viruses, and other particles and gels. In 2005, an interlaminar distance of 17.9 Angstroms, or six layers of water, still seems to be stable in hydrated montmorillonite (Odriozola & Aguilar, 2005). Clay continues to be studied in relation to nuclear waste disposal, so the effects of surfaces on water's properties haven't been entirely excluded from science. The interfacial water in clay has special catalytic properties that make it interesting to many researchers (Anderson, 1970)

Bernal's and Perutz' conformity to the 1950s rejection of long range forces and an ordered structure of water represented the dominant ideas in physics and physical chemistry, but many people (with very little financial or institutional support) were continuing to study the structure of water, both in the bulk phase and near surfaces, as in cells. Philippa Wiggins, Albert Szent-Gyorgyi, Carlton Hazlewood, Freeman Cope, and Ray Damadian were among the most active proponents of the importance of structured water in living cells. Walter Drost-Hansen showed that water near surfaces (vicinal water) is several percent less dense, and has a greater heat capacity, than bulk water, and that bulk water undergoes transitions at certain temperatures that alter its effects on enzyme reactions.

The question regarding the nature of the forces at surfaces or interfaces affects how we think about everything, from life to nuclear energy. The political and economic implications of "non-local energy" (which is most obvious at surfaces) have at times led to organized campaigns to discourage research in those areas. When Alexandre Rothen found (beginning in 1946) that enzymes and antibodies had non-local effects, several prestigious publications claimed to show how he must have been mistaken: The films he used must have been porous, despite his demonstrations of their continuity.

The methods he developed at Rockefeller Institute quickly became standard for accurately measuring very thin films. In the early 1970s, a GE employee, Ivar Giaever, visited Rothen's lab to learn his methods. Shortly after his visit, he demonstrated his "new method" to the press. I saw an article about it in Science News, and wrote them a short letter, pointing out that the method had been developed and used by Rothen much earlier; they printed my note, which could be seen as a criticism of the author of the news article. About a week later, I got a letter from Rothen, thanking me for writing to the magazine; he said they had refused to publish his own letter explaining the situation, including his interactions with Giaever during the visit. I assume that the magazine felt some kind of pressure to protect Giaever and GE from an authoritative accusation of scientific dishonesty.

In 1968 when I began studying biology at the University of Oregon, the professor of microscopy, Andrew Bajer, posted a display of dozens of micrographs, with explanatory captions, along the halls near the entrance of one of the science buildings. The one that interested me most showed orderly rows of regularly formed objects on a smooth surface. The caption described it as clusters of sodium atoms, deposited from vapor, on a film of a polymer (formvar, I think), under which was a quartz crystal. The caption noted that the sodium atoms had condensed in a pattern representing the crystal structure of the underlying quartz. Although Rothen's work involved proteins deposited from solution, rather than sodium atoms deposited from vapor, Bajer's image illustrated visually the projection of the forces of crystal structure through an amorphous film. This seemed to be a graphic representation of Polanyi's adsorption potential, a force acting on atoms in the space near a surface, as opposed to Langmuir's local atomic force that didn't reach beyond the first layer of atoms. The long range order in this case arranged atoms geometrically, while Rothen's preparations showed a "projected" specificity, but of a more complex sort.

Just a few months later, someone who knew of Stephen Carter's demonstration that fibroblasts will migrate on a glass slide coated with a gold

film, toward areas of greater thickness of the metal, did a similar experiment, but with a formvar film between the gold and the cells. The cells still migrated up the gradient, toward the area of thicker gold under the film. The reaction to that publication was the same as the reaction to Rothen's work 20 years before, the formvar films contained holes, and the cells were reaching through the film to touch the metal surface, sort of like kids peeking around a blindfold when they aren't supposed to be watching. I didn't understand how the holes would explain anything, even if there were holes and if the cells had put out many long filopodia to reach through the film, but in fact making a formvar film is a very standardized technique. They can be made "holey," or like a very open net, or they can be made solid, just by choosing the concentration of the polymer used. The difference is very clear, under an electron microscope, but the professors needed an excuse for dismissing something they didn't want to understand. Further work was discouraged by their ridicule.

In Russia, GE had very little influence on the acceptability of ideas in science, and Boris Deryagin continued (from the 1930s until 1990) to study the properties of water near surfaces. In 1987 his group demonstrated that cells can clear particles from a space around themselves, extending more than a cell's diameter away. This distance is similar to the cell free zone in flowing blood adjacent to the walls of arterioles, which is probably the result of multiple interacting forces. At present, processes such as cell adhesion of leukocytes and stem cells (and tumor cells) to the blood vessel wall and movement through the blood vessel into the tissues (diapedesis) is explained in terms of adhesion molecules, disregarding the plausible effects of long range attractive or repulsive forces. Clumping or sludging of red blood cells occurs when the organism is failing to adapt to stress, and could be reasonably explained by a failure of protective repulsive fields. These fields are developed and maintained by metabolism, primarily oxidative energy metabolism, and are modified by endogenous regulatory substances and external conditions, including electromagnetic and electrical fields.

100 years ago, Albert Einstein was a major influence in popularizing the "only local" dogma of atomic interactions. (His work led directly to "quantum physics," but he never accepted its irrational implications.[1] I don't think he ever considered that the assumptions in his [atomic-quantized] theory of the photoelectric effect were the problem.) One charged atom is completely neutralized by its association with an oppositely charged atom, and the force is described by the inverse square law, that the force decreases with the square of the distance between point charges, meaning that the force is very strong at very small distances. However, a physical ***surface***, a plane where one substance ends and another begins, follows different rules.

Different substances have different electron affinities, creating a phase boundary potential, a charged layer at the interface. (Electrical double layers at interfaces are important in semiconductors and electrodes, but biologists have carefully avoided discussing them, except in the very narrow context of electrodes.) The electrically active surface of a substance, even though it's made of atoms and electrons, projects its electrical field in proportion to its area. This principle is as old as Coulomb's law, but the habit of thinking of electrical charge on the atomic scale seems to make people forget it. It's exactly the sort of space-filling field that Polanyi's adsorption isotherm describes. It's also involved in crystal strength and elasticity as studied by Polanyi, in piezoelectricity, and in generation of semiconduction in amorphous materials, as used in Stan Ovshinsky's processes.

Long range structural and electronic interactions produce "antenna" effects, which are sensitive to very weak fields, whether they originate inside or outside of the organism. Magnetobiology is often treated as a pseudo-science or pathological science, because "real science" considers heating and chemical bond reactions to be the only possible effects of low energy fields or radiation. Solco Tromp, beginning in the 1930s, showed that cells behave like liquid crystals, and that liquid crystals can respond to very low electrical and magnetic fields.

If the adsorption potential structures the water in its region of space, this interfacial water is now a new *phase*, with different physical properties, including new catalytic properties, such as those recognized by the clay investigators (which increased its ability to dissolve the clay minerals).

Several versions of Langmuir's Pathological Science talk have been published, some of them adding new examples, including "polywater." Langmuir died in 1957, and the first example of polywater was observed by N.N. Fedyakin was observed in 1961. When finely drawn quartz or Pyrex glass capillary tubes (with inside diameter of up to a tenth of a millimeter) are suspended in a container with the air pressure reduced, above a container of distilled water, so that they are exposed to pure water vapor at room temperature, after a period of an hour or more (sometimes days or weeks were required) a small drop of liquid condenses inside some (a small percentage) of the capillary tubes. Above some of the original drops, a second drop sometimes appeared, that would enlarge as the first drop shrank. This separation of water into two fractions was itself anomalous, and the upper drop was found to be denser than normal water. Many people began studying its properties. Fedyakin found that its thermal expansion was greater, and its vapor pressure lower, than ordinary water. Others found that it had a higher refractive index, viscosity, and surface tension, as well as greater density, than ordinary water. Birefringence (the splitting of a beam of light into two rays when it passes through an ordered material) was observed in the anomalous water, and this usually indicates the presence of a polymer (Fedyakin, et al., 1965; Willis et al., 1969; Lippincott, et al., 1969) or crystallinity. The water associated with clay is also birefringent (Derjaguin and Greene-Kelly, 1964), and its properties are different when the clay absorbs it from the vapor phase or from liquid water.

Hysteresis is a lag in the behavior of a system, resulting when the internal state of the system is altered by an action, so that it responds differently to a repetition of that action; it's the memory of a system that exists only when the system has internal structure. For example, a gas has relatively little hysteresis. Perfect elasticity is one extreme of an ordered solid, but most solids have some hysteresis, in which the deformed material fails to spring back immediately. Hysteresis of adsorption can be seen at the edges of a drop of water on a tilted surface, with a steeper contact angle on the newer contact at the lower edge, showing a reluctance of the water to wet a new surface, a lower contact angle where the drop is pulling away from the upper surface, a reluctance to break the contact. The same is seen at the edges of an evaporating-shrinking drop, or a growing drop. Everyone perceives this memory function of water.

Boris Deryagin studied both the elasticity and the hysteresis of water near surfaces, and both approaches showed that it contained internal structure. Many dogmatic professors denied that water could show elasticity or "memory," because of their interpretive system/mental rigidity.

When Fedyakin got the help of Deryagin's lab in analyzing the anomalous material, many different methods of purifying the glass and the water and the vessel were tried, and its properties were analyzed in many different ways. When Deryagin first described the material at a conference in Europe, there was great interest, and eventually hundreds of people began investigating it.

A British laboratory was the first to get a sample of Deryagin's material in 1966, and their tests confirmed Deryagin's.

The US Bureau of Standards, having the best analytical instruments in the world (including a microscope spectrometer), studied it carefully. They (Lippincott, Stromberg, Grant, & Cessac, 1969) found that its bonds were stronger than those in ordinary water, and they compared its absorption spectrum (by computer) with those of 100,000 known substances, and found that it corresponded with nothing previously known. It didn't have the absorption band of normal water. When it evaporated, it left no visible residue, and it turned into ordinary water when heated. They concluded that the physical structure that would best fit its absorption spectrum was a polymerized form of water, so they called it "polywater." Later, Lippincott and others (Page, et al., 1970; Petsko, 1970) did proton magnetic resonance analyses that

showed a difference of polywater from normal water in the hydrogen bonding, a "deshielding" of the protons, meaning that the electrons were arranged differently in the molecules.

In 1969 there were many threats to the dominant paradigm, and many people were demanding a change in the government's funding priorities. The public excitement about polywater following the many confirmations of its existence was disturbing to the defenders of the paradigm. Philip Abelson, the chief editor of Science magazine, used the magazine to further his political beliefs.

Denis Rousseau, a young researcher at Bell Labs (who now writes about pathological science), published a series of articles in Science describing his tests of polywater. He played tennis until his tee-shirt was soaked with sweat, then extracted and concentrated the sweat into a small gummy pellet. He reported that the infrared spectrum of the sweat concentrate (largely sodium lactate) was very similar to that of polywater. One of the techniques he used to identify impurities (electron spectroscopy) requires a high vacuum, so there couldn't be any normal water present. The water associated with ionic impurities is driven off at low temperatures compared to the temperature needed to decompose the anomalous water.

Although Rousseau's "explanation" was ludicrous, it was just the thing the professors needed to prevent further challenges to their paradigm. Although Deryagin published more evidence of the purity of the anomalous water in 1972, by 1973 the mass media, including Science magazine, were saying that polywater didn't exist, and that Deryagin had admitted that he was mistaken. But polywater was Lippincott's term, and what Deryagin said was that silica was the only impurity that could be identified in the anomalous material.

There are many antecedents to anomalous water in the literature. In the 1920s, W.A. Patrick of Johns Hopkins and J. L. Shereshefsky at Howard university investigated the properties of water in fine capillary tubes and found that the vapor pressure wasn't the same as that of normal water. (This is what would have been expected, if Polanyi's adsorption isotherm had been accepted.) The density of water in clay has been found to be slightly less than normal. This water bound to clay requires a high temperature to eliminate, similar to the decomposition temperature of polywater. The catalytic properties of interfacial water in clay are recognized, causing it to solublize components of the clay. So it's hard to imagine that there wouldn't be some silica in the material formed in quartz or glass capillary tubes.

The only thing pathological about the polywater episode was the extreme effort that was made to stigmatize a whole category of research, to restore faith in the old doctrine that insisted there are no long range ordering processes anywhere in the universe. The successful campaign against polywater strengthened the mainstream denial of the evidence of ordering in interfacial and intracellular water, kept the doctrine of the lipid bilayer cell membrane alive, and up until the present has prevented the proper use of MRI scans in medical diagnosis.

In 1946, while the government was studying the way nuclear fallout was influenced by the weather, a group at GE, led by Langmuir, began experimenting with weather control by means of "cloud seeding." Langmuir observed that the energy in a cloud system was greater than that in an atomic bomb, and that by seeding clouds in Europe, disastrous weather effects could be created in the Soviet Union. The GE group convinced the Pentagon to become involved in weather control. (The physicist Ross Gunn was transferred directly from work on the atomic bomb to direct the cloud seeding project.) In one of Langmuir's seeding experiments, he claimed that he had changed the direction of a hurricane moving toward the U.S. When a young researcher pointed out that the weather service had predicted exactly that change of direction, based on the temperatures of ocean currents, Langmuir became angry, and told the man that he wasn't going to explain it to him, because he was too stupid to understand.

Langmuir's attitude toward science was exactly what GE wanted; his career and reputation were part of the corporation's public relations and business plan. Science was whatever GE thought

was good for their business. That science was pathological, sometimes by Langmuir's own defining features, most of the time by the effects it has had on society. The Manhattan Project was central to GE's business plan, and when the bomb project was completed GE and the Atomic Energy Commission found that the same subsidies could be used to develop nuclear generators of electricity. Following Edison's pioneering work with x-rays, x-ray imaging machines had become very profitable for GE. It was important to assure the public that medical, industrial, and military radiation was well understood, well controlled, safe, and essential for the general welfare. In their view, if every woman could have access to GE's x-ray mammograms, for example, almost all breast cancers could be cured. The radiation exposure from living near a GE nuclear power generator is infinitesimal compared to living in Denver or flying in an airplane. (There is some discussion of these issues in my January, 2011 newsletter, "Radiation and growth.") Public relations involves everything from "basic research" to television advertising.

If nuclear energy is as safe as the industry and governments say it is, the reactors should be located in the centers of large cities, because transmitting electric power long distances is presently wasting 50% of the power (Hirose Takashi, The Nuclear Disaster that could destroy Japan...and the world, 2011). Admiral Rickover, influential advocate of nuclear power, said "...every time you produce radiation, [a] horrible force [is unleashed,] and I think there the human race is going to wreck itself. [We must] outlaw nuclear reactors" (January, 1982 congressional testimony) Helen Caldicott says Fukushima is many times worse than Chernobyl. The radioactive cesium in German mushrooms and truffles hasn't decreased 25 years after Chernobyl, and the German government is spending increasing amounts to compensate hunters for the wild boars (who eat truffles) that must be disposed of as radioactive waste.[2]

General Electric sent its condolences to the people of Japan, and said the reactors of that design had functioned well for 40 years; they didn't mention that Unit I at Fukushima had been scheduled to be shut down on March 26, 2011, the end of its 40 year life expectancy. In late March, as the accident continued, Tepco applied for a permit to build two new reactors at the Fukushima site. In the US, the government continues its loan guarantee policy to subsidize new reactor construction.

After many years of working with his metalized slides, Alexandre Rothen found that their activity, the strength of their long-range influence, varied with a 24 hour cycle, and that their activity could also be destroyed or restored by putting them in a magnetic field, parallel or perpendicular to the surface. Around the same time, a Russian biochemist, Simon Shnoll, noticed that there were cyclic changes in well defined enzymic reactions. Like Rothen, Shnoll did experiments that showed that the earth's motion (relative to the stars) affected measurements in the laboratory, even measurements of alpha particles produced by nuclear fission. Organized matter, whether it's cellular or in the crystalline solid state, is susceptible to surrounding conditions.

In 1971 or '72 I learned of H.C. Dudley's idea of a "neutrino sea," that he suggested might be equivalent to the "luminiferous ether" that had previously been used to explain light and electromagnetism. I wrote to him, asking if he thought neutrinos could be involved in biological ordering processes by resonating with matter under some circumstances. He had been developing a theory, in which atomic nuclei might interact with a neutrino "ether," in ways that could affect the decay rate of the unstable isotopes, and so it didn't seem unreasonable to him that biological structures might also interact with neutrinos. In October, 1972, he published a purely theoretical article in which he explained that nuclear reactors might under some conditions become dangerously unstable. I had earlier seen a newspaper article about an experiment by a physicist, J.L. Anderson, in which radioactive carbon-14 didn't follow the normal rules of random decay, when the isotope was incorporated into an oil, which was spread in a monolayer on a metal surface. By chance, Anderson's experimental article was published simultaneously with Dudley's theoretical article, though neither one knew of the other's work.

Nearly all physicists said his results weren't possible, because the small forces involved in adsorbing an oil to a metal surface were infinitesimal compared to the force needed to cause nuclear reactions. Over the next few years, Dudley and others did some experiments that appeared to confirm Anderson's results, showing that the rate of nuclear reactions can be modified by mild changes in the physical state of the unstable elements.

Anderson's and Dudley's work didn't get much attention from the public, so there was no need for the defenders of the dominant paradigm to attack it. There was no financial support for continuing their research.

Behind the industries' assurances that "low level" radiation is safe, whether it's ionizing radiation, microwave or broadcast frequency electromagnetic radiation, is their reductionist approach to physics, chemistry, and biology. Those doctrines no longer have the prestige that they once did, but their pathological, authoritarian "science" culture is being sustained by the influence of corporations on mass culture.

With the institutions of research and education controlled by pharmaceutical, military and industrial interests for their own benefit, fundamental progress in knowledge is a threat to the system.

NOTES

1. From Einstein's 1926 letter to Max Born: "Quantum mechanics is very worthy of regard. But an inner voice tells me that this is not yet the right track. The theory yields much, but it hardly brings us closer to the Old One's secrets. I, in any case, am convinced the He does not play dice." Quoted in P. Busch and G. Jaeger, "Unsharp quantum reality," 4 May 2010.

2. None of the major institutions in the US are providing basic information about protection from Fukushima's radioactive fallout. Eating foods produced before the arrival of the radioactive rain, feeding old foods to chickens and milk animals, and keeping your metabolic rate high, are the main defenses. Eventually, fertilizing crops with mined minerals, and enriching the atmosphere with carbon from coal will dilute the radioactive isotopes from the nuclear accidents.

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Ray Peat's Newsletter

It is difficult to get a man to understand something when his salary depends on his not understanding it. Upton Sinclair

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The GABA system, defenses, and tissue renewal

Inhibition is an active process, that isn't limited to the effects of specific inhibitory nerves. In recent decades, the amino acids gamma-aminobutyric acid (GABA) and glycine (alpha-aminoacetic acid) have been identified as "inhibitory transmitters," acting on specific receptor proteins to inhibit a nerve or muscle.

This has led to increasing understanding of some sedative and anti-convulsive drugs, but it neglects the real biological nature of inhibition and excitation. The amino acid "transmitters" are just part of a much larger system of cell regulation.

To understand healing and regeneration and other developmental and formative processes I think it's necessary to consider the issues of cellular and organismic stability and instability, inhibition and excitation, in the most thorough and general way.

Cell interactions generally involve mutual stabilization. Nerves stabilize muscles, muscles stabilize nerves, and nerves stabilize other nerves. Losing their normal intercellular communications, cells become hypersensitive and hyperactive.

When an excess of stimulation threatens to damage a tissue, processes of inhibition can restore stability. But when cells are damaged irreparably, stimulation can induce other cells to grow and multiply to replace the lost cells. The growth continues until inhibitory processes are restored.

Protective inhibition is one of the most important principles in biology. Heart disease, cancer, anxiety, allergies, epilepsy, degenerative nerve diseases, endocrine disorders, inappropriate inflammation and shock all involve defects of protective inhibition.

The agents of protective inhibition increase survival, along with mental abilities and metabolic rate. Too often the excitants suppress energy production while increasing the need for energy, leading to impaired functions and failure of restorative processes.

For thousands of years people have understood the value of herbal sedatives, soporifics, and anti-convulsants, but modern neurology's ideological commitments have retarded the scientific development of therapies to enhance protective inhibition.

J.C. Bose, working in England and India at the end of the 19th century (radio, microwave, vegetable electricity, the electric response of inorganic substances), showed that plant cells and animal cells have very similar reactions, and that similar processes of excitation, fatigue, and recovery also occur in substances such as metal. Drugs and poisons could be shown to have effects on plant material and metals,* analogous to their effects on animals.

Michael Polanyi's work with crystals in the 1920s showed that merely wetting a surface affected the physical properties of the whole crystal.

His understanding of sensitivity, irritability, fatigue, memory and other biological processes disturbed the academic biologists, who were committed to a certain biological doctrine in which membrane electricity and genes explained everything, and had nothing directly to do with general properties of matter.

C.S. Sherrington in England, and S. Ramón y Cajal and R. Lorente de Nó in Spain developed the idea of the synapse as a point of interaction between nerve cells, which formed the basis for reflexes. A nerve would transmit its excitation to a muscle or another nerve in an all-or-none manner, that is, the reaction, if it happened at all, didn't correspond to the strength of the stimulation. The reductionist ideology was already, at the beginning of the 20th century, reducing biological interactions to simple yes or no, black or white, terms. The infinite complexity of the material substrate was eliminated from direct participation in the scheme of life by definition.

Like Descartes, Sherrington and his followers saw reflexes as something separate from consciousness. "Between reflex [automatic] action and mind there seems to be actual opposition. Reflex action and mind seem almost mutually exclusive - the more reflex the reflex, the less does mind accompany it." "The mental action lies buried in the brain, and in that part most deeply recessed from outside world that is furthest from input and output."

Later in the 20th century, biologists were still identifying consciousness with graded processes, that are too subtle to be accounted for by the all-or-none synaptic interactions of nerves.

In 1863, I.M. Sechenov had already published a book, Reflexes of the Brain, arguing that all aspects of the mind, including thoughts and feelings, directly involve nervous activity.

A Russian biologist, Vvedensky (1902), demonstrated that weak stimuli and strong stimuli applied to a nerve produced very different effects in the muscle activated by the nerve. "Wedensky *[German spelling]* found that at a certain stage in the fatigue or narcosis of a muscle-nerve preparation, a series of strong or rapidly recurring stimuli may produce a small initial contraction only (Anfangszuckung), whereas a series of weak or slowly recurring stimuli produce a continued tetanus." (J Physiol. 1913 July 18; 46(4-5): 384-412. Wedensky inhibition in relation to the `all-or-none' principle in nerve. E. D. Adrian.)

Another Russian biologist, P.N. Nasonov, using a variety of cell types, including algae, showed that an excessive stimulation that weakened a cell's ability to respond electrically also weakened its resistance to other environmental factors, and that the right kind of stimulation could increase the cells' resistance to stress. These ideas were expanded and applied to human health issues by the cardiologist F.Z. Meerson, whose laboratory investigated the protective and therapeutic effects of the complex multi-level inhibitory anti-stress system.

The Sherrington tradition, the synapse-membrane all-or-none school of neurology, was complemented by the hormone-receptor-gene-activation school of endocrinology, and by parallel reductionist approaches to embryology. None of these traditions produced anything useful, except in the sense that the receptor doctrine was perfectly suited to pharmaceutical advertising.

The all-or-nothing reflex doctrine reinforced an interpretation of the cell in which a barrier membrane at the cell surface momentarily opens when it's appropriately stimulated, allowing excluded sodium ions to enter, modifying the electrical field and causing a reaction that "propagates along the

nerve like a line of falling dominoes." As Gilbert Ling has pointed out, that doctrine isn't based on real science--for example, the resting membrane doesn't exclude sodium ions. Many things account for the fact that it continues to be taught, but I have talked about that previously. The fact that "membrane depolarization" makes it easy to conceptualize propagation of the excited state as an all-or-none process appeals to the reductionist mentality. But more than 70 years ago, A.V. Hill's measurements of heat production during nerve activity demonstrated that the wave of excitation passes through the entire substance of a nerve, rather than being a matter of "falling dominoes" in the superficial plasma membrane.

It is in the substance of the nerve cytoplasm itself that the protective inhibitory processes occur. In the all-or-none membrane theory in which reflexes are produced by synaptic events, the inhibitory GABA receptors are described as membrane receptors. The basic theory of membrane receptors is that, since the membrane is a barrier, the receptor allows hormones or transmitter molecules to act on the cell without having to enter the cell.

But when a molecule resembling an inhibitory steroid was made water soluble, so that it couldn't enter cells, it was unable to activate the GABA receptor associated with the membrane. When it was presented to the receptor from the cytoplasmic side, however, it was able to modify the GABA receptor. (Akk, et al., 2005.) The normal oil soluble neurosteroids tend to remain in the cells when they are made there, or to enter them spontaneously from the bloodstream, so the postulated function of "membrane receptors" would seem to be wrong. The GABA receptor has been found to associate with the internal cytoskeletal proteins. This is significant, because the glutamate transporter, that participates in restoring inhibition, has recently been found to be associated with a cytoskeletal protein (GFAP) (Sullivan, et al., 2007). This protein is known to be induced by progesterone.

The membrane theory is an attempt to explain the coordination of events that happen in a cell when it is stimulated. The different phases of heat change observed by Hill and others subsequently can only be explained as a phase change in the bulk of the cellular substance, not just a ripple in a superficial lipid film. Different molecular conformations and associations have different levels of organization, that represent structural energy, and different arrangements are separated by small energy barriers. Mutual stabilization of molecular systems gives way to a cooperative phase transition and the establishment of a new organization at a slightly different energy level when stimulation overcomes the energy barrier. The domino analogy is inadequate because the change is three dimensional. Proteins, lipids, sugars, water and ions participate in these cooperative structural changes.

A student of Pavlov's, P.K. Anokhin, discussed a variety of reasons for believing that the information transmitted by the activated state of an axon was complex, rather than a single binomial bit. Since his time many kinds of information have supported and enriched that view. Cellular interactions are always complex, and the all-or-none reflex is an extremely misleading abstraction.

Drugs and natural regulatory substances associate with certain proteins, and those proteins are identified as their "receptors." Since the technique of "knocking-out" the genes for specific receptors has been developed, it has become apparent that the regulatory substances are often able to act without the protein that had been known as the receptor. (For example, Reddy and Apanites, 2005.) Other proteins may then be identified as additional receptors. Occasionally, the

condition of the phospholipids and fatty acids, or the preceding state of the cell, is recognized as having a crucial role in the cell's response. But this holistic view hasn't been useful to the pharmaceutical industry.

Interacting cells are participating in a developmental process, in which their structures and metabolisms are regulating themselves in relation to their situation, which is influenced by events in the life of the whole organism. An organism's anticipation and learning contribute to the renewal of tissues and resistance to stress. Unavoidable stress damages or kills nerve cells, and the resulting mobilization of defenses can lead either to successful defense and recovery, or inadequate defense and chronic disease.

Once the protective function of inhibition is recognized, there are many things that can be done to support the organism's recuperative processes.

Pavlov and his followers began applying the principle of protective inhibition to medicine, and it has been used to treat neuroses, brain injuries (even "brain death"), and various organic diseases. Pavlov observed that individual differences in nervous stability could cause the therapeutic dose of a sedative to vary several-fold. Prolonged sleep was found to be a very powerful therapy, that could even reverse age-related changes, but drugs such as the barbiturates were too toxic for extensive use of the therapy. Sleep induction by electrical brain stimulation was investigated as an alternative. Subsequently, Meerson's group investigated the metabolic and biochemical factors involved in protective inhibition. Although Meerson's research focused on the heart, the factors he identified apply to other organs and tissues. The progressive commercialization of medical research, however, has submerged those integrated organismic approaches to therapy.

Using the general approach of Pavlov and Meerson, it's now possible to achieve a high degree of protective inhibition without using toxic drugs, but it's important to minimize the chronic factors that create a susceptibility to uncontrolled excitatory states.

The toxic effects of excessive stimulation involve suppression of respiratory energy production. Excitation releases fatty acids from tissue phospholipids, and the polyunsaturated fatty acids (PUFA) increase excitation, decrease the inhibitory actions of the GABA system, and interfere with energy production by the mitochondria, leading to the wasteful conversion of glucose to lactic acid. Excitation increases the production of free radicals by the mitochondria themselves (Duan, et al., 2007). Just eliminating most PUFA from the diet decreases the risks of excitotoxicity.

DHA and arachidonic acid increase the excitatory effect of glutamate on its receptor (Yeh, et al., 1995), and decrease the uptake of glutamate by the protein that binds it to stop the excitatory process (Yu, et al., 1986). These fats cause swelling of mitochondria and cells, and increase vascular permeability. Saturated fats don't have those excitatory effects.

Fish oils and other omega -3 oils are being promoted as treatment for many diseases, especially heart disease, arthritis and other inflammatory diseases, and depression. They do have an antiinflammatory effect, at least in the short term, partly associated with their inhibition of prostaglandin synthesis, but their antiinflammatory effects have been found to result from their oxidized products (Chaudhary, et al., 2004), which have many toxic effects. Although claims are made regarding their beneficial effect on the circulatory system, there are good reasons to think that they contribute to atherosclerosis (for example, Wang and Oram, 2002, 2005). And they suppress the immune system and thyroid function.

The PUFA (especially the omega -3 fatty acids) spontaneously decompose into a variety of toxins, and arachidonate is also enzymically converted into prostaglandins, some of which exacerbate the excitatory damage (Pepicelli, et al., 2005); aspirin's neuroprotective effect (Riepe, et al., 1997) is probably partly caused by inhibiting prostaglandin synthesis. Besides the prostaglandins, other mediators of inflammation including nitric oxide and interleukins are produced by excessive excitation, as cells lose their ability to retain magnesium, and to control excitatory intracellular calcium.

Nitric oxide, associated with unbalanced excitation, is involved in the nerve damage of epilepsy, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease. An energy deficit increases excitation and cellular calcium uptake, increasing nitric oxide synthesis (Schulz, et al., 1997). Nitric oxide increases the ratio of glutamate to GABA ("the excitotoxicity index"), (Demchenko & Piantadosi, 2006), while lowering mitochondrial energy production.

The PUFA increase the susceptibility to excessive serotonin in the nervous system. One of the functions of the GABA system is to inhibit serotonergic nerves (Calogero, et al., 1988; Kaura, et al., 2007). Eating a diet with a very low tryptophan content, and lacking PUFA, can support that function of the GABA system. The tea amino acid, theanine, suppresses serotonin by supporting the effects of GABA. Three of the major types of antidepressant also protect against glutamate/aspartate-induced nitric oxide formation and nerve cell damage (Li, et. al., 2006).

It's important not to confuse the process of inhibition with psychological depression, which often involves an inability to inhibit the stress responses. The GABA system restrains the production of cortisol, which is typically increased in depression. GABA-supporting drugs that had been used to treat epilepsy are turning out to have antidepressive, mood-elevating effects.

The diazepam type of antianxiety, antiseizure drug activates the GABA system, and this system is intimately involved with the synthesis of steroids. Several varieties of that type of sedative increase the synthesis of the neurosteroids, derived from progesterone. Progesterone and some of its metabolites protect the mitochondria, while acting with GABA to increase the state of inhibition.

During the menstrual cycle, the GABA system is weaker during estrus, when estrogen's effect is high. Progesterone is associated with a higher level of GABA, and the two substances have many of the same effects on behavior.

Estrogen's excitatory effects can be seen in all types of tissue. In the brain, it tends to increase physical activity and loquacity, to increase the susceptibility to seizures, and sometimes to cause chorea, involuntary random jerking and writhing movements.

It is antagonistic to the GABA system, and promotes the action of excitatory transmitters, and increases formation of nitric oxide and prostaglandins. In cancers that are promoted by estrogen, GABA, like progesterone, inhibits cell division. It is an antiproliferative agent in normal tissues, too, opposing estrogen's effects and supporting progesterone's.

Drugs (such as piracetam) that promote GABA's effects are called "nootropins," or cognitive enhancers, and have been used to treat brain damage and mental retardation. GABAergic agents also protect the thymus gland and improve immune functions.

The first serious approach of the pharmaceutical industry to treating Alzheimer's disease was based on increasing the excitatory action of acetylcholine. When it became apparent that those drugs weren't helpful,

there was a less publicized trial of some drugs that block the effects of acetylcholine. If white doesn't work, they try black. The industry's function, exercised through medical and science journals, and medical schools and universities, is to sell new products, and that has often made it necessary for the industry to suppress approaches that would make their products unnecessary. As the head of a drug company told me, a drug that cures quickly isn't a good drug; a good drug is one that the patient has to keep taking for the rest of his life.

Progesterone's inhibitory function was already well established in the 1940s, by the work of Selye and Lipshutz, for example. In the 1950s and 1960s its effects on brain development and intelligence were established. In vitro studies showed that it was a nerve growth factor, and it was identified as a hormone that caused new brain cells to develop in an area of birds' brains as their ability to sing developed. Katherina Dalton's clinical experience supported the animal work which showed that prenatal exposure to higher levels of progesterone improved mental functioning later in life.

Progesterone supplementation can sometimes cause complete recovery from dementia and motor neuron diseases.

After many years of animal experiments showing that progesterone promotes recovery from traumatic brain damage (Cutler, et al., 2007; Stein, 2007), it is now being used to treat people following severe brain injury (Wright, et al., 2007).

Neither progesterone nor GABA stimulates cell multiplication, yet they improve the regenerative process. Their effects are the result of preventing premature cell death, and promoting normal differentiation and maturation. In various kinds of degenerative brain disease, the connective tissue glial cells in the brain become too numerous, while the nerve cells decline. Excitatory processes cause new cells to be formed, and with the proper energetic and inhibitory support the new cells can mature into functional nerves, that maintain or restore the existing systems and functions.

Certain kinds of excitation cause new nerve cells to be formed (neurogenesis). The enzyme that liberates arachidonic acid (phospholipase A2, which also releases docosahexaenoic acid DHA) from tissue structures, creates a type of phospholipid that is slightly more water-soluble and mobile because of the removal of that fatty acid. These are called lysophospholipids, because they were originally identified as a substance that lysed red blood cells. The enzymes that produce them are activated by many things, including free radicals, increased calcium, and the shift of balance toward excitation (Birkle, 1992), away from dominance of the GABA system.

The lysophospholipids stimulate, among other things, neurogenesis (Fukushima, 2004; Harada, 2004; Ishii, et al., 2003; Dubin, et al., 1999). The arachidonic acid that is liberated in its formation excites cells, in a process that can get out of control if the inhibitory GABA system is weak. It can produce gliosis from excessive stimulation of cell division combined with a lack of the factors such as GABA needed for maturation into nerve cells, and it can kill nerve cells, by interrupting their energy production. The accumulation of this and related fatty acids with aging is a problem.

The DHA and other polyunsaturated fatty acids released by cellular excitation cause mitochondrial damage and edema, but saturated fatty acids don't have those effects (Chan and Fishman, 1980, 1982; Chan, et al., 1988; Hillered and Chan, 1988, 1989).

Alexis Carrel, with a famous experiment begun in 1912, showed that animal tissues kept in culture dishes with frequent (daily)

changes of the growth medium didn't age, and he suggested that changes in the fats in the body accounted for aging. Lately the gene-technology people have said fraud was involved in Carrel's experiments, but many other kinds of experiment produced similar results. For example, Hans Selye found that frequent changes of fluid prevented aging of tissue growing inside an implanted capsule.

Polezhaev's discovery that mammalian tissues can be induced to regenerate by the presence of degenerating tissue (which releases the breakdown products of phospholipids and proteins) is consistent with the recent demonstrations that stem cell growth is activated by fatty acids and phospholipids.

The saturated fats, rather than simply lacking the toxic and excitatory properties of the polyunsaturated fats, are being shown by many types of research to have protective, inhibitory, and restorative actions.

The medium chain triglycerides (MCT, usually made from coconut oil) are easily oxidized by mitochondria, and are often used to produce ketosis, to prevent seizures. A high-fat diet has been used since about 1920 to control epilepsy, but there is no generally accepted explanation for its effect. A ketogenic diet produces acetone, acetoacetate, and beta-hydroxybutyrate ("ketone bodies") and these are protective against seizures (Rho, et al., 2002). Besides providing energy to mitochondria, hydroxybutyrate is structurally close to GABA. Other close analogs, gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol, clearly act as regulatory substances, rather than as mere energy sources, though mitochondrial energy supply is an important issue in seizures. Even acetate itself is protective (Urion, et al., 1979).

A feature common to many antiseizure chemicals is a series of saturated carbon atoms, for example valproic acid (2-propylpentanoic), valeric acid (pentanoic acid), dipropylacetic acid, isoleucine (2-amino-3-methylpentanoic acid), leucine (2-amino-4-methylpentanoic acid).

The main difference between metabolism of glucose and metabolism of fat for energy is that fat can't be metabolized into lactic acid, while glucose and fat can both be metabolized to carbon dioxide. When mitochondria are damaged, cells compensate by producing and excreting lactic acid.

Alzheimer's disease has been described as "diabetes of the brain," because the demented brain uses glucose and oxygen very slowly. The easily metabolized medium chain triglycerides can improve mental functions in Alzheimer's patients (Reger, et al., 2004).

Although diabetes is described as an inability to use glucose, diabetics usually have increased lactate in their blood, indicating that glucose is being used wastefully, at the same time that some energy is produced from fat. Mitochondria damaged by chronic exposure to PUFA have a low rate of oxygen use and energy production.

In old age, and sometimes in younger people, mitochondria lose some of their DNA, and are unable to produce the proteins needed for full metabolic activity. In younger people, a type of mitochondrial defect causes seizures and lactic acidosis. The production of lactic acid tends to raise the intracellular pH (especially when carbon dioxide isn't being produced) while it tends to lower the blood's pH. High intracellular pH is excitatory. The "genetically" defective mitochondria can be replaced by genetically normal mitochondria if the ketone bodies are provided (Santra, et al., 2004). A similar restoration of normal mitochondria can be achieved in old people's muscles through a program of "concentric" contractions.

Other GABAergic agents are able to functionally restore damaged mitochondria,

but in these studies, the quality of the DNA wasn't investigated. Piracetam intensifies oxygen consumption in damaged mitochondria, for example following injury or oxygen deprivation, especially in older animals. The restoration is permanent, so in this case the substance isn't acting just as a more easily metabolized source of energy, as was believed to be the mechanism in the case of the ketone body supplement.

Many people still believe that increasing oxygen consumption necessarily increases free radical activity and shortens the life-span, and that the life extension produced by caloric restriction results from reduced oxygen consumption. The fact that estrogen suppresses mitochondrial oxygen consumption is being used to justify using it to treat aging and dementia. But caloric restriction doesn't reduce oxygen consumption per gram of tissue, and sometimes increases it. Uncoupling mitochondria, so that they consume more energy without producing more ATP, appears to produce an extension of lifespan approximately equal to the increased rate of energy and oxygen consumption (data discussed in Speakman, 2003). Increasing the metabolic rate has effects similar to restricting calories. Supplementing thyroid, increasing saturated fats such as MCT and coconut oil, and restricting polyunsaturated fats, can increase the metabolic rate.

Piracetam (like other GABAergic agents) very effectively decreases lipid peroxidation (Novikov, et al., 1996), despite increasing metabolic activity. While decreasing oxidative damage and increasing ATP production, it also lowers the activity of the cells' important antioxidant enzymes (Keil, et al., 2006). When a cell isn't being damaged, those adaptive enzymes aren't required to be so active. (Many publications argue that certain products are "beneficial because they increase the antioxidant enzymes," but in fact almost any kind of injury will increase those protective enzymes.)

If mitochondria aren't damaged, for example in healthy young animals, piracetam doesn't greatly increase their activity. It simply restores them when they are damaged.

The mitochondria, besides producing energy and regulating calcium and other minerals, are the source of the GABAergic steroids. Since mitochondria contain "valium receptors" or GABA receptors, their high concentration in the region of synapses has probably sometimes been interpreted as showing "membrane receptors." But wherever they are, mitochondria are powerful agents of cellular interactions and regulation.

The carbon dioxide produced by mitochondria is involved in regulating ions and cellular electrical polarization, and protecting against free radicals. The energized and polarized cell retains magnesium and potassium, and excludes sodium and calcium. Increasing magnesium favors the protective inhibitory state, and is sometimes given intravenously to stop seizures. Adequate sodium in the diet is necessary for efficient retention of magnesium, and sodium is also required for the binding of glutamate. Lithium can replace sodium in activating glutamate removal (Menaker, et al., 2006), and it protects the brain against excitotoxicity (Chuang, 2004).

Breathing carbon dioxide has been used to stop seizures, and the drug, acetazolamide, which increases the body's retention of CO2, is sometimes used for epilepsy. Increased carbon dioxide protects the brain against a variety of factors (e.g., Simon, et al., 1993), and is probably involved in glutamate uptake.

Niacinamide, one of the B vitamins, happens to have GABAergic sedative activity, but it also has two other important effects. It can suppress lipolysis and lower circulating free fatty acids, reducing their interference with the use of glucose, and when the

mitochondria are already damaged, it can reduce the formation of lactic acid, by allowing the sugar to be fully oxidized. Forming the coenzyme NAD, niacin is responsible for maintaining an appropriate balance between oxidation and reduction (as the main cellular reductant), protecting cells from oxidative stress. (Shen, et al., 2003; Singh, et al., 2005; Kang, et al., 2006; Watanabe, et al., 2006; Kao, et al., 2007; Su, et al., 2007). The glutamate transporter must be kept in the reduced state to bind glutamate and stop the excitatory process (Trotti, et al., 1997).

Maintaining an adequate supply of glucose is directly protective against excitotoxicity (e.g., Flavin, et al., 1993), and helps to prevent stress reactions systemically.

Thyroid hormone (which has a reciprocal relation to estrogen) produces many relaxant effects, such as rapid relaxation after the Achilles tendon reflex contraction, reduced blood pressure, and deeper sleep, but its supportive effects on the GABA system are seldom considered in relation to therapies. It is essential for producing carbon dioxide, the neurosteroids, and ATP. Magnesium is retained in cells largely by its association with ATP, and it helps to keep the ATP level high. Thyroid is needed for preventing excessive estrogen stimulation, and for controlling adrenaline and serotonin. But it also directly interacts with the GABA system, supporting the protective inhibitory functions (Zamoner, et al., 2006; Gilbert, et al., 2007; Ortiz-Butron, et al., 2003).

Inhibitors of estrogen synthesis are being considered for use in controlling epilepsy (Reddy, 2007), but aspirin and progesterone and thyroid can produce similar results.

When mitochondria are functioning fully, either glucose or saturated fats can safely provide energy. Some glucose or saturated fat can be converted to polyunsaturated fats, that can be used as regulators or signals, for example to activate the formation of stem cells. But those PUFA don't create disruptive cascades of increasing excitation or inflammation or excessive growth, and, from the evidence of animals that are fed fat free diets, or diets lacking omega -3 and omega -6 fatty acids, they aren't toxic to mitochondria.

When a healthy cell is excited, the mitochondria become more active, and their energy needs may exceed the amount of glucose available, leading to the formation of ketone bodies. Glucose deprivation seems to be a fundamental signal of stress, and the formation of ketone bodies is possibly the most primitive defensive reaction to stress. They protect nerves from excitatory oxidative damage (Noh, et al., 2006), inhibit mitochondrial production of reactive oxygen species during excitation (Maalouf, et al., 2007) and inhibit tumor growth and lactate production (Magee, et al., 1979). Increased thyroid hormone can increase ketone formation (Riou, et al., 1980; Bartels and Sestoft, 1980).

The idea of synaptic membrane receptors often leads people to think of cellular inhibition in terms of raising a cell's threshold for producing an all-or-none membrane response to stimulation. But the inhibitory and excitatory systems interact at all levels of function and structure, reciprocally modifying each other.

In response to signals for excitation or inhibition, for example, the quantity of GABA and GABAergic steroids such as progesterone will change, in response to increases or decreases in the enzymes that produce or eliminate them, and changes in concentrations of precursor molecules. The quantity and sensitivity of the various types of "receptor" will change. Proteins that bind and inactivate GABA and other regulators will change in quantity and effectiveness. The rate at which energy is produced will change, along with the rates of cellular reconstruction and

decomposition. The cells' metabolic changes will produce signals that affect adjoining cells and the organism's physiological processes, including circulation, respiration, and readiness for stress.

In the "normal" course of aging, good tissues atrophy, and may be partly replaced by fibrotic tissues, and in that environment, tumors and disorganized structures of various kinds develop. The highs and lows, the daily cycles of mental and physical activity, tend to be leveled, as the ability to produce metabolic energy declines.

The polyunsaturated fats suppress energy production, and that suppression is aggravated by their excitatory or inflammatory effects, which lead to increased excitation by other intrinsic factors such as estrogen, cytokines, serotonin, and peptide hormones, that intensify the problem of maintaining energy production. Stimulation, without corresponding appropriate inhibition and adequate energy, skews the path of development, toward aging and sickness.

When each cell is fully energized and stabilized, it is sensitive and responsive to its surroundings, supporting the organism's adaptability.

Although caffeine is a stimulant that can offset the sedative effects of GABA, it also functions as a neuroprotectant, protecting against some of the effects of glutamate (Chinopoulos, et al., 2004). It is also a very good source of two other protective factors, magnesium and niacin. "French-roast" (dark) coffee is an especially rich source of niacin, which might be responsible for the "French paradox," the low incidence of heart disease in a country that doesn't follow the AHA's "heart protective diet."

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March 2011 newsletter:

Serotonin: Effects in disease, aging and inflammation

Interpreting medical publications requires some skills that aren't needed for understanding more strictly scientific reports, because medical writing often takes into account the fact that physicians spend most of their time interacting with the public, rather than studying. The public's understanding of medicine is shaped by "public relations," by the introduction of words and concepts that frame the argument. (The linguist George Lakoff summarized the essence of public relations by observing that people reject facts that are outside their view of reality, their mental framework.) Television and public schools now frame the worldview of the affluent cultures, according to the needs of the ruling powers. Long before specific prescription drugs could be advertised directly to consumers, the medical and pharmaceutical industries were creating a favorable frame for their products.

Many years ago, public relations experts used expensive opinion polls to judge the effectiveness of their efforts, but now there is a convenient way to see how the general public is thinking**:** Wikipedia, the internet encyclopedia. The success of corporate advertising can be seen in their recent article on serotonin, which says "It is a well-known contributor to feelings of well-being; therefore it is also known as a 'happiness hormone' despite not being a hormone."

The culture that has happy and unhappy hormones was a culture in which each hormone had a receptor, a substance in a cell which, when its ligand was bound to it, made the cell do something. Although that culture still has influence in the 21st century, discoveries made between 1940 and 1970 showed that those mechanical ideas of receptors didn't reflect biological reality. Albert Szent-Gyorgi and the Pullmans showed that the electronic qualities of molecules determined their functions, and Szent-Gyorgyi showed that the state of the cell, tissue, and organism governed the effect of hormones and drugs. In the 1960s, substances with very different biological effects, such as acetylcholine and adrenaline, were shown to be selectively bound to the same cellular site in some cells. It was primarily the drug industry that created and sustained the specific receptor doctrine. That doctrine suited the recognition of their public relations-marketing experts, that successful advertising had to be directed at the sixth-grade educational level. The ideas of bioelectronics and context-sensitive molecules, like morphogenetic fields, were just too complicated to sell well.

Although metaphorical thinking can be creative and productive, metaphors mustn't be taken literally. The identification of multiple types of receptor for a given natural substance involves the use of different substances as metaphors or similes for the natural substance. That type of pharmacology is slowly being replaced by an attempt to understand state-dependent sensitivities. The energetic state of a cell, and of the whole organism, determines the meaning of events and conditions, such as the presence of the "regulatory substances."

The receptor culture can be tentatively disregarded when thinking about the history of serotonin. In the 1930s Vittorio Erspamer identified an amine in the intestine, that caused the intestine to contract. Then a group in England extracted an amine from serum that caused blood vessels to contract, and identified its chemical nature. Later, Erspamer showed that the intestinal amine and the vascular amine were chemically the same. The English group who had identified the substance by extracting tons of beef blood, wanted to find sensitive ways to assay it for further studies, and in 1951 they gave a sample to a pharmacologist, John Gaddum, who tested its effects on tissues including blood vessels and rat uteruses.

Gaddum tested the serotonin in combination with a variety of other drugs, including ergot derivatives, that he knew acted on smooth muscles, and very soon observed that LSD blocked the effects of serotonin. Since he knew that LSD produced mental effects (Sandoz had distributed samples of it to researchers in 1947), he reasoned that the brain might also contain serotonin, and by 1952 was able to

demonstrate that it does contain small amounts of it. A couple of years later he suggested "that the mental effects of lysergic acid diethylamide are due to interference with the normal action of this HT [5-hydroxytryptamine, serotonin]." At the Rockefeller Institute in New York, Woolley and Shaw also saw the antagonistic effects on smooth muscle, and drew similar conclusions about the brain. Erspamer (Renic. sc. farmital. **1**, 1, 1954) showed that LSD was a highly effective antagonist against the antidiuresis caused by serotonin (enteramine).

Around the same time, in the early 1950s, several people recognized that the symptoms produced by administering an excess of serotonin were similar to those experienced by people with intestinal tumors called argentaffinomas or carcinoid tumors, which are usually in the small intestine or appendix. The normal intestine contains about 95% of the serotonin in the body (and the brain normally contains only about 1%), and in the normal person only about 1% of the dietary tryptophan is converted to serotonin. But in an advanced case of carcinoid, 60% of the tryptophan can be turned into serotonin. Especially if the tumor has invaded the liver, the serotonin won't be destroyed by the liver in the usual way, and will circulate in the bloodstream at high levels, producing symptoms of flushing, sweating (sometimes dark-colored), diarrhea (serotonin stimulates small intestine smooth muscle, but inhibits the large [Bennett & Whitney, 1966]), nausea, anxiety, reduced urination, muscle and joint pains, and, in late stages, very often cardiovascular disease (especially inflammation, fibroma and calcification of the valves in the right side of the heart) and aggressive behavior (Russo, et al., 2004) and psychosis.

Testing Gaddum's idea of antagonism between LSD and serotonin in humans, Montanari and Tonini found that intramuscular injections of serotonin antagonized the psychological effects of LSD. Other drugs, especially other ergot derivatives, were more successful than LSD in blocking the effects of serotonin (Dubach and Gsell, 1962). There have been suggestions that pregnancy hormones could control serotonin excess (McCullough and Myers, 1965). Since estrogen promotes serotonin, progesterone is likely to be the protective factor (Donner & Handa, 2009; Hiroi, et al., 2006; Berman, et al., 2006; Bethea, et al., 2000).

More recently (Spigset, et al., 2004), it was found that LSD binding to a presumed serotonin receptor was low in carcinoid patients, supporting the idea of antagonism between the substances, but in the older studies symptoms, rather than competition for binding to certain proteins, were the focus of attention. The effects produced by injections and oral doses of synthetic serotonin, and of substances that block the synthesis of serotonin, were studied in both animals and humans. When a symptom such as clotting, flushing, or diarrhea is produced by serotonin itself, or prevented by a blocker of serotonin synthesis, "receptors" aren't an issue.

Aldous Huxley was one of the first people to think about the general biological meaning of drugs such as LSD. Referring to the ideas of Henri Bergson and William Blake, he suggested that the brain usually acts as a filter, or "reducing valve," to make us disregard most of the information we are receiving through our senses, and that the psychedelic drugs temporarily remove the filter, or open the sensory reducing valve. Bergson had suggested that the filter was a practical measure needed to allow us to focus on practical survival needs; Blake had suggested that the doors of perception were kept closed for cultural reasons.

Some recent reviews have discussed the evidence supporting the serotonin system as primarily inhibitory and protective (Anne Frederickson, 1998, Neil Goodman, 2002). Goodman describes the serotonergic system as one of our "diffuse neuroregulatory systems," and suggests that drugs such as LSD weaken its inhibitory, filtering effect. (Jacobs, 1983, 1987: by changes in the effects of serotonin in the brain, produced by things that affect its synthesis, release, catabolism, or receptor action.) LSD depresses the rate of firing of serotonergic nerves in the raphe nuclei (Trulson and Jacobs, 1979) causing arousal similar to stimulation of the reticular formation, as if by facilitating sensory input into the reticular formation (Bowman and Rand, 1980).

In European culture, some people--e.g., Plato, Descarte, Locke, Eccles, probably even B.F. Skinner--have believed that mind and body are essentially different things (analogous to computer hardware and its programs), while another tradition--Blake, Lamarck, Darwin, C.L. Morgan, Pavlov, Reich, C.R. Cloninger, for example--has emphasized the continuity of consciousness and character with the body.

Understanding the authoritarian personality has been an important issue in the 20th century. Wilhelm Reich used some old ideas about the nervous system that were current near the beginning of the century, and Cloninger (1995) and others (Netter, et al., 1996, Ruegg, et al., 1997, Gerra, 2000), toward the end of the century, were able to incorporate the newer information about the serotonergic-dopaminergic antagonisms. In this newer view, high serotonin production causes behavioral inhibition and harm avoidance, which are traits of the authoritarian personality, while antiauthorians tend to have "novelty seeking" personalities, with high dopamine and low serotonin functions.

In the 1960s, experimenters put electrodes into a chicken's optic nerve, and when the chicken saw a checkerboard pattern, they could measure a patterned electrical activity in the nerve. Without the light stimulating the retina, the nerve was quiet. But when they gave the chicken LSD or similar chemicals, they recorded patterned electrical activity in the nerve, in the absence of external stimulation. Around the same time, other experimenters showed that retinal fatigue quickly desensitized the retina, preventing the transmission of impulses to the brain, except when the light pattern corresponded to something familiar, showing that impulses from the brain are always involved in renewing, in patterned ways, the sensitivity of the retina.

The latter experiment shows that everyone's perception involves an outward-directed activity of the brain, and the experiments using the chemical stimulants suggested that the intensity of the outward-directed action can vary.

The inhibitory serotonergic "harm avoidance" system, and the opposing excitatory activating "novelty seeking" systems are constantly being influenced by many factors, including nutrition, hormones, environmental challenges and opportunities, social interactions, seasons, and the rhythm of night and day alternation.

Several kinds of research are now showing that the effects of the environment on the serotonergic system and its antagonists can influence every aspect of health, not just the personality.

For example, there have been suggestions that early life isolation of an animal can affect its serotonergic activity and increase its anxiety, aggression, or susceptibility to stress (Malick and Barnett, 1976, Malick, 1979, dos Santos, et al, 2010), and these effects are associated with increased risk of becoming depressed, and developing organic problems. Animals kept in darkness (or with blurring lenses) become nearsighted, as the eyeball grows longer under the influence of increased serotonin, and the eyes are protected against myopia by serotonin antagonists (George, et al., 2005). The incidence of myopia is increasing, at least in countries with industrialized economies, and is more common in females.

Migraine headaches are also increasing in incidence. By the end of the 1950s, it was widely accepted that migraine headaches and associated symptoms including nausea and visual disturbances were caused by an excess of serotonin, and antiserotonin drugs of various types were being used for treatment. In one of the early studies of the use of LSD in psychotherapy, some of the patients noticed that their chronic headaches had stopped. Cluster headaches have also responded well to LSD and similar drugs (Sewell, et al., 2006).

Women have migraines more often than men do, and they tend to occur in association with ovulation or menstruation. Estrogen inhibits monoamino oxidase, MAO, especially the A form that is most active in detoxifying serotonin, and it increases the enzymes that control the rate of serotonin synthesis. During serotonin excess, the veins and capillaries of the pia mater are engorged with blood, while circulation to

the brain generally is depressed. Visual symptoms are probably produced by contriction of arterioles, while the pain is associated with engorged veins. Progesterone activates the MAO-A, and has other antiserotonin effects on blood vessels and nerves.

Recently (Shansky, et al., 2010; Figueiredo, et al., 2007), females have been found to be more susceptible to stress, and to have reduced uptake of serotonin (prolonging its effects), which increases glucocorticoids and ACTH. Kendler, et al. (2005) have found that people with reduced serotonin uptake are more susceptible to stress-induced depression.

The increase of inhibitory serotonin with stress and depression is probably biologically related to the role of serotonin in hibernation, which is an extreme example of "harm avoidance" by withdrawal. A diet high in polyunsaturated fat increases the tendency to go into hibernation, probably by increasing the brain's uptake of tryptophan. When this is combined with an increasingly cold environment, the form of MAO that removes serotonin decreases its activity, while the form that removes norepinephrine increases its activity. The metabolite of serotonin, 5-HIAA, decreases, as the effect of serotonin increases.

In experiments to investigate the mechanism of hibernation, animals were injected with serotonin, at different environmental temperatures. In a cool environment, the serotonin caused their temperature to fall, by decreasing their heat production, and increasing their loss of heat (by causing vasodilation in the skin, "flushing"). In a hot environment, serotonin can cause the animal's temperature to rise.

Serotonin can reduce the production of energy by inhibiting mitochondrial respiratory enzymes (Medvedev, 1990, 1991), and by reduction of oxygen delivery to tissues by vasoconstriction. It also appears to interfere with the use of glucose (de Leiva, et al., 1978, Moore, et al., 2004).

The brains of people with Alzheimer's disease have a decreased ability to metabolize glucose, and high cortisol contributes to the altered glucose metabolism, and to the destruction of nerve cells. People with Cloninger's "harm avoidance" personality trait, which is closely associated with serotonin (Hansenne, et al., 1999), are more likely to develop dementia (Clément, et al., 2010). These observations are consistent with the stress-susceptibility of people with high serotonin exposure, and to the effects of cortisol on nerves and glucose-derived energy production.

Researchers in Brasil have suggested that the serotonergic system facilitates conditioned fear, while inhibiting the fight or flight reaction, and that this can protectively limit the stress response (Graeff, et al., 1996). "5HT systems reduce the impact of impending or actual aversive events. Anticipation of an aversive event is associated with anxiety and this motivates avoidance behaviour" (Deakin, 1990). In a stressful situation, the serotonergic nerves can prevent ulcers. In other contexts, though, increased serotonin can cause ulcers.

The protective, defensive reactions involving serotonin's blocking of certain types of reaction to ordinary stresses, are similar to the effects of serotonin in hibernation and in Alzheimer's disease (Mamelak, 1997; Heininger, 2000; Perry, et al., 2002). In those extreme conditions, serotonin reduces energy expenditure, eliminating all brain functions except those needed for simple survival. These parallels suggest that improving energy production, for example by providing ketones as an alternative energy source, while reducing the stress hormones, might be able to replace the defensive reactions with restorative adaptive nerve processes, preventing or reversing Alzheimer's disease.

One of the factors promoting excess cortisol production is intestinal irritation, causing absorption of endotoxin and serotonin. Fermentable fibers (including pectins and fructooligosaccharides) support the formation of bacterial toxins, and can cause animals to become anxious and aggressive. Fed to horses, some types of fiber increase the amount of serotonin circulating in the blood. Grains, beans, and other seeds contain fermentable fibers that can promote intestinal irritation.

The liver has several ways to detoxify endotoxin and serotonin, but these can fail as a result of poor nutrition and hypothyroidism.

The lung can bind and destroy any excess serotonin that reaches it. A lack of carbon dioxide makes platelets release their stored serotonin, and it probably has the same effect in the lung endothelial cells. Without being able to bind the serotonin, the enzyme (indoleamine 2,3-dioxy- genase) would be unable to destroy it.

An excess of tryptophan in the diet, especially with deficiencies of other nutrients, can combine with inflammation to increase serotonin. Polyunsaturated fatty acids promote the absorption of tryptophan by the brain, and its conversion to serotonin. (A "deficiency" of polyunsaturated fat decreases the expression of the enzyme that synthesizes serotonin [McNamara, et al., 2009).

Some fruits, including bananas, pineapples, and tomatoes, contain enough serotonin to produce physiological effects in susceptible people.

Besides avoiding foods containing fermentable fibers and starches that resist quick digestion, eating fibrous foods that contain antibacterial chemicals, such as bamboo shoots or raw carrots, helps to reduce endotoxin and serotonin. Activated charcoal can absorb many toxins, including bacterial endotoxin, so it is likely to reduce serotonin absorption from the intestine. Since it can also bind or destroy vitamins, it should be used only intermittently. Frolkis, et al. (1989, 1984) found that it extended median and average lifespan of rats, beginning in old age (28 months) by 43% and 34%, respectively, when given in large quantities (equivalent to about a cup per day for humans) for ten days of each month.

The amino acid theanine, found in tea, has been reported to decrease the amount of serotonin in the brain, probably by decreasing its synthesis and increasing its degradation. This seems to be the opposite of the processes in hibernation. Progesterone, thyroid, and niacinamide (not nicotinic acid or inositol hexanicotinate) are other safe substances that help to reduce serotonin formation, and/or accelerate its elimination. (Niacinamide seems to increase serotonin uptake.)

To provide usable energy to the over-stressed brain (and heart), R.L. Veech has advocated the use of ketones, but the pure chemicals are expensive to make. An easily available and inexpensive source of ketones (in the form of ketoacids, which can be converted to amino acids if they aren't needed for energy) is the juice extracted(with a centrifugal juicer) from raw potatoes, which also contains proteins and other nutrients. The juice can be scrambled like eggs, and is usually tolerated even by very debilitated people.

Hypothyroidism is a very common cause of increased serotonin (e.g., Henley, et al., 1998), and if the thyroid hormone is supplemented until symptoms are resolved, it's likely that the serotonin will have been normalized.

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Ray Peat's Newsletter

If others had not been foolish, we should be so. William Blake

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Endotoxin, stress, depression:
Serotonin, starches, fatty acids, and antidotes

Increasingly, intestinal serotonin is being recognized as a factor in osteoporosis, migraine, irritable bowel syndrome, appendicitis, and cancer. From ancient times until about 100 years ago, the bowel had a very important place in medical practice, with purgatives and enemas being recommended for headaches, persistent coughs, seizures, and many chronic diseases. Pavlov studied the digestive system as a way to understand the mind, because it's where we interact most closely with the environment.

Up to Pavlov's time, traditional medicine thought in terms of achieving balance in the organism, using metaphors such as the four humors (phlegm, blood, yellow bile and black bile) and the four personality types---phlegmatic, sanguine, choleric, and melancholic.

In western Europe and the US during the 19th century, divisions in medical doctrine began to appear between traditional, "empirical" practitioners and advocates of a new "rational," reductionist allopathic doctrine who were coming to believe that disease had its origin in cells and their defects of form or function. These "scientific physicians" began a major propaganda campaign to ridicule blood-letting and purging as examples of the unscientific practices of their competitors. The idea of internal toxins itself was ridiculed. A gastroenterology professor (Walter C. Alvarez) used his newspaper column to argue against the old ideas, for example that toxins absorbed from the intestine caused headaches. He described putting wads of cotton into the rectums of his medical students, and a considerable number of them developed headaches while the cotton was in place. That, he asserted, disproved the idea that absorbed toxins were the cause of headaches. It didn't really disprove anything, but it contributed to the culture that was discouraging the use of laxatives. Russian researchers, who were still working in Pavlov's holistic tradition, found that inflating a balloon in an animal's intestine didn't have any observable effect in a normal animal, but when the animal's blood sugar was lowered, the stretching of the intestine would produce a wide range of symptoms, from asthma to seizures. It is likely that some of Alvarez's students had low blood glucose, and were more susceptible than others to the abnormal stretching of the rectum.

Inflammation of the bowel used to be recorded frequently as the cause of death of older people, but now it's seldom mentioned in autopsy reports as the cause of death, if it's mentioned at all.

Hans Selye had noticed that intestinal bleeding was a standard feature of being sick, and it became a defining feature of his concept of stress. Old people sometimes get ulcers in their colon or rectum, adjacent to lumps of hardened fecal material. Selye devised animal experiments, in which he showed that an interference with blood circulation that normally didn't produce serious harm, would cause similar (stercoral) ulcers, and also paralysis of the hind legs, if he injected serotonin into the animal. If the anti-serotonin drug, cyproheptadine, was given to the animal before the serotonin, they were protected. The ulcers required the combination of restricted blood circulation, excess serotonin, and the presence of feces in the lower intestine. Without the serotonin, the other two factors failed to produce the ulcers (1966). In a previous experiment, he had demonstrated that the combination of impaired circulation with serotonin would cause severe muscular dystrophy (1965).

Selye's research group showed how closely the digestive system and the nervous system interact, but they didn't go very far in exploring the effects of diet on the nervous system.

Just friction, or scratching or stretching the intestine is enough to cause it to release serotonin into the bloodstream. Serotonin increases the permeability of the intestine and blood vessels, and so is likely to be a major cause of the absorption of endotoxin (and other harmful material) during intestinal irritation or stress. The biological meaning of serotonin might be very different without endotoxin, but that hasn't been investigated.

Bacterial endotoxin increases serotonin release from the intestine, and increases its synthesis in the brain (Nolan, et al., 2000) and liver (Endo, 1983). It also stimulates its release from platelets, and reduces the lungs' ability to destroy it. The formation of serotonin in the intestine is also stimulated by the lactate, propionate and butyrate that are formed by bacteria fermenting fiber and starch, but these bacteria also produce endotoxin. The inflammation-producing effects of lactate, serotonin, and endotoxin are overlapping, additive, and sometimes synergistic, along with histamine, nitric oxide, bradykinin, and the cytokines.

There have been some studies showing that bacterial fermentation in the intestine can cause many symptoms, including behavioral changes.

For example, a diet of soy protein increases aggression in monkeys (Simon, et al., 2004) and chickens (McKeegan, et al., 2001).

When various fermentable carbohydrates were fed to rats, they became anxious and agressive, and these changes in behavior corresponded to the fermentation of these materials by bacteria in the lower intestine, with the production of lactic acid (Hanstock, et al., 2003, 2004).

Dietary fiber has been promoted for a long time, and for many reasons---John Harvey Kellogg argued that it prevented dirty thoughts, the cholesterol people argued that it would lower cholesterol, Denis Burkitt, in the 1970s, suggested that it could prevent colon cancer. When Burkitt visited the US and saw that oat bran was being recommended, he commented that the main fiber in the African diet he had studied was potato. By the 1980s, studies in animals were showing that some kinds of fiber, including **oat bran, pectin, corn bran, metamucil, undegraded carrageenan, agar, psyllium, guar gum, and alfalfa,** were carcinogenic, increasing the incidence of colon cancer, and possibly ovarian and breast cancer (Toth, 1984, Jacobs, 1986, Goodman, et al., 2002).

Many advocates of increasing dietary fiber argue that butyric acid is a protective factor produced by bacterial decomposition of starch and fiber, and it does (at least in vitro) sometimes cause cancer cells to differentiate into normal cells. However, it accelerates the growth of intestinal cells, and when that is combined with toxins it might act as a tumor promoter. The lactic acid produced by bacteria and by the inflamed intestine itself is now recognized as an important factor in the development of cancer.

The upper part of the small intestine is sterile in healthy people. In the last 40 years, there has been increasing interest in the "contaminated small-bowel syndrome," or the "small intestine bacterial overgrowth syndrome." When peristalsis is reduced, for example by hypothyroidism, along with reduced secretion of digestive fluids, bacteria are able to thrive in the upper part of the intestine. Sugars are very quickly absorbed in the upper intestine, so starches and fibers normally provide most of the nourishment for bowel bacteria.

Besides avoiding gums and other "soluble fiber," and starches that aren't quickly digested, there are several things that can protect against the toxic effects of bacterial degradation products. Beans are famous for their gas-producing polysaccharides, but all grains and vegetables and firm under-ripe fruits contain starches that resist our digestive enzymes, but that can provide food for bacteria. Undercooked starch, and starches combined with enzyme inhibitors (including polyunsaturated fats), tend to be fermented by bacteria. New technology in the orange juice industry has converted normal pulp to soluble fiber that supports bacterial fermentation.

A high ratio of calcium to phosphorus reduces the breakdown of fibers, and this probably contributes to some of the protective effects of a

large amount of calcium in the diet, for example reduction in the incidence of bowel and ovarian cancer.

A few plant fibers have a high proportion of cellulose, that resists bacterial attack, combined with antibiotics that suppress bacterial growth, but in most grains and vegetables, and many fruits, cellulose is combined with fibers that support bacterial growth. Fats, especially saturated fatty acids, have antiseptic properties, and when they are combined with starches and fibers they help to suppress bacterial growth. Their effects can be seen in various ways, including protection against the anxiety caused by fermentation (Prasad and Prasad, 1996).

Thyroid hormone increases digestive activity, including stomach acid and peristalsis, and both thyroid and progesterone increase the ability of the intestine to absorb sugars quickly; their deficiency can permit bacteria to live on sugars as well as starches.

Pavlov's and Anokhin's understanding of the organism in terms of its integration of perceptions of the actual situation, including its needs, and its projection of the possibility of satisfying those needs, gives us a way to understand some of the ways that our digestive system interacts with our physical health and our moods and emotions. Anokhin, in analyzing Pavlov's Reflex of Purpose and Exploratory Reflex, described the way that the cortex of the brain creates a model of the world, including information about the present state of the organism. Anokhin called this model of the situation the Acceptor of Action, because it was the framework for evaluating behavior. A properly functioning organism is always projecting or imagining future possible situations, and projecting or imagining its actions in those situations, evaluating the possibilities.

Any particular external situation can create stress or not, depending on what it means to the individual. The perception of a possibly good outcome mobilizes the creative adaptive abilities, in a functional system that includes an external goal and relevant physiological processes; the failure to see possibility in the situation--anticipating failure rather than success--demobilizes the systems of adaptation, and the excitation caused by unsatisfied needs produces generalized catabolic processes.

As the organism prepares to enact these imagined possible futures, it mobilizes the appropriate resources, activating some systems and inactivating other systems, constructing, consuming and redistributing its own substance, while assimilating substances from the environment. The anabolic hormones, such as thyroid, and the tissue-catabolic hormones such as cortisol, act both locally and systemically, according to various regulatory processes, mainly nervous processes. A functional system is created for achieving the goal. As the organism achieves its purposes or adapts, the catabolic hormones will subside.

Sensory nerves in the intestine contribute to the organism's assessment of the situation--the Acceptor of Action--and motor nerves adjust the state of the intestine and other organs. The interplay between the state of the intestine and the assessed state of the stressful situation determines whether the individual will withdraw (often with incontinence of the bowel and bladder) or persist and struggle to adapt.

Defensive aggression is probably a response intermediate between fearful giving up and confident achievement. When a rat is restrained, held down on its back, it quickly develops ulcers, but if it has a stick to bite, it is very resistant to the formation of the ulcers. The ability to do something with a defensive meaning prevents the excessive production of serotonin and its consequences, such as increased production of cortisol and other stress hormones, and disturbance of cirulation and energy production. Endotoxin and prostaglandins activate these same systems, and progesterone and aspirin are among the protective factors that can oppose those effects.

When physical and mental activity are intensified to meet an adaptive crisis, the adrenergic sympathetic nervous system optimizes muscular energy production, but inhibits the digestive system. In the state of anxious-helpless withdrawal, the parasympathetic and serotonergic systems demobilize the active neuro-skeletomuscular systems, and activate the bladder, intestine and stomach, tending to empty the

contents by causing diarrhea, vomiting, and urination. Serotonin reduces energy production in muscles; this is probably related to the muscular dystrophy it produced in Selye's experiments, and the myopathy produced by tryptophan (Castot, et al., 1991). Antiserotonin drugs are used for controlling diarrhea and vomiting, and some of them are protective against ulcers (Ramesh, et al., 2009).

Chronically elevated cortisol is commonly seen in depressed people, but giving a supplement of cortisol is effective in relieving depression. Both cortisol and the pituitary corticotropic hormone that stimulates its production, ACTH, have some antidepressant effects, and they inhibit the hypothalamic corticotropin release hormone, CRH. CRH is more directly associated with depression than cortisol is, and it by itself activates many inflammatory processes, including the release of histamine, cytokines, and nitric oxide. CRH is promoted in the hypothalamus (and in many other tissues) by inflammation, endotoxin, serotonin, interleukins, and prostaglandins, but also by the perception of unavoidable difficulties.

Besides cortisol, progesterone and androgens are internal factors that decrease the activity of CRH. Estrogen and hypothyroidism increase its activity.

The convergence, interaction, and summation of inflammatory molecules with the perceived meaning of a situation is a subject carefully avoided by those who think of the organism as a sum of its molecules and cells. They accept that transmitter molecules and receptor molecules regulate behavior, and influence perception, but they can't explain how understanding and interpretation can make the profound differences in feeling, behavior, and biochemistry that they in fact do make.

The model of nerves as on-off switches, governed by the state of their membrane, has made the problem of integrating meaning with chemistry seem impossibly complex. In recent years it has been recognized that nerves can produce or respond to more than one kind of signal, but few people have understood nerve cells in a way that could allow individual cells to handle complex and subtle signals, and to make rational judgments based on such signals. P.K. Anokhin, G. Albrecht-Buehler and a few others have observed the importance of recognizing cellular complexity, and the ability of cells to integrate complex information. The cell physiology of Gilbert Ling and Albert Szent-Gyorgyi demonstrated the basis on which these complex integrating processes can be understood.

Nerves and muscle cells should be considered together, because they respond to many things in similar ways. The membrane people don't like to think that nerves have any contractile properties, but in fact they do twitch slightly when stimulated, showing that it is the entire cytoplasm that responds to information, not the hypothetical plasma membrane. When they are overstimulated, they swell, as muscles do when they are fatigued. When a muscle is stretched while it's trying to contract (as in running downhill; this is called "eccentric contraction") it becomes inflamed, and the structural damage can be cumulative. By exercising muscles with "concentric contractions," allowing them to shorten against resistance, the cellular damage can be repaired.

Stretching a nerve causes some metabolic changes similar to the muscle in eccentric contraction, but nerves are normally protected against injuries of that sort. However, very intense stimulation of a nerve fiber can disrupt its internal structure, causing "beading," an intermittent clumping of the nerve filaments and microtubules along the axon, as if the internal structure is contracting in segments, while the overall axon doesn't contract. With intense stress, the beaded fiber can separate into individual pieces, like droplets of cytoplasm, instead of the elongated cylinder. Long before stress causes it to disintegrate in that manner, it is likely that it causes it to lose its functional coherence.

The excessive stimulation of a cell increases its internal alkalinity, causing it to take up more water. The mediators of inflammation, such as CRH, serotonin, and endotoxin cause cell swelling and increased alkalinity. CRH and endotoxin can increase the susceptibility to seizures, but they can also block the ability of cells to respond to normal stimulation.

Serotonin, as an alkaloid, is bound and inactivated by acidic cells. Carbon dioxide, produced by respiration, normally keeps cells slightly acidic. Hyperventilation, or the production of less carbon dioxide and more lactic acid, causes serotonin to be released from platelets and other cells where it has been inactive, allowing it to enter other cells where it has its characteristic effects, increasing lactate, decreasing ATP (Assouline-Cohen, et al. 1998, Koren-Schwartzer, et al., 1994), increasing pH, and stimulating contraction or mitosis.

One of the very neglected mechanisms of serotonin's action is its ability to activate carbonic anhydrase, a class of enzymes that convert carbon dioxide to bicarbonate, and tend to increase the alkalinity of cells. Inhibitors of carbonic anhydrase are currently being investigate for their ability to stop the growth of cancer cells and to permit their recovery of normal functions. One of the carbonic anhydrase inhibitors, acetazolamide, has been used for many years to treat epilepsy, glaucoma, migraine, sleep apnea, mountain sickness--and even psychosis (Inoue, et al., 1984).

Serotonin's effects appear to be the result of its action on the microtubules or other elements of the cell skeleton (Bianchi, et al., 2003, Grass, et al., 2004), which are the main integrating elements of the cell. Chronic disturbance of the microtubules and neurofilaments, with inflammation and impaired energy production, is characteristic of Alzheimer's disease.

If the internal and external causes of stress converge, additively, on the cell's internal communication and integration system, then the basic resistance of the organism to stress can be increased by any of the factors which oppose the signals of stress.

Carbon dioxide, progesterone, and thyroid act on many of the factors that interfere with our ability to handle stress constructively. A diet that reduces fermentation and endotoxin, with an abundance of calcium--fruit, milk, and cheese, for example--can help to shift the balance away from lactic acid, estrogen, and serotonin, toward carbon dioxide, progesterone, and thyroid.

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Ray Peat's Newsletter

"Unthinking respect for authority is the greatest enemy of truth." --Albert Einstein

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Rosacea, Inflammation, and Aging: The Inefficiency of Stress

> ***Rosacea, or acne rosacea, has been defined as "vascular and follicular dilation involving the nose and contiguous portions of the cheeks . . ." that may involve persistent erythema with hyperplasia of sebaceous glands.***
>
> ***Stedman's Medical Dictionary 23rd edition.***

Light-skinned people, especially women between the ages of 30 and 50, sometimes develop a persistent redness of their cheeks and nose. It may begin as a tendency to flush excessively, but the blood vessels can become chronically dilated. Similar processes occur in dark-skinned people less frequently.

The eyes are sometimes involved, with redness of the exposed areas (conjuctival hyperemia). New blood vessels develop in the area, and the flow of blood through the affected tissue is greatly increased. The tissues become thickened and fibrotic, with the multiplication of fibroblasts and the increased deposition of collagen.

The cornea normally receives its oxygen from the air, and its nutrients from the aqueous humor. As rosacea of the eye develops, the blood vessels surrounding the cornea become increasingly visible, and, especially on the inner (nasal) side of the eye, the vessels tend to enlarge and become tortuous. Rhinophyma, or potato nose, has been described as a late development of rosacea.

Too often, the medical reaction is to give the condition a name, and to distinguish its variants as if they were different problems, and then to use the most direct means to eliminate the problem they have defined.

A typical attitude is that "Rosacea is an enigmatic disease with multiple exacerbations and remissions, and, unfortunately, treatment is directed toward symptomatic control rather than cure" (Randleman).

Lasers or other radiation, caustic chemical abrasion, surgical planing and dermal shaves, and other forms of surgery may be used to destroy the superficial blood vessels, and to reduce the enlarged nose or other irregularities. A few decades ago, when rosacea was believed to be the result of a local infection, antibiotics were used to treat it, and some of them, including tetracycline, helped. It was discovered that some antibiotics have anti-inflammatory actions, apart from their germicidal effects, and now it is very common to prescribe the chronic use of tetracycline to suppress symptoms.

Rosacea, and the fibrotic changes associated with it (pingueculae and pterygia in the eyes, rhinophyma of the nose, etc.), are much more than "cosmetic" issues, involving the skin and eye surface. If the invasive proliferation of blood vessels can be prevented, it's important to do that, because, for example, pannus/neovascularization of the cornea can seriously impair vision.

But possibly the strangest thing about the relationship of the medical profession to rosacea is that its essential features, invasive neovascularization and fibrotic growth, are of great interest when they occur elsewhere, and many physiological processes are known to regulate the growth of blood vessels and fibroblasts, but nearly all the attention given to rosacea and rhinophyma concerns control of symptoms for cosmetic effect. Rosacea is a physiological problem that deserves consideration in the light of all that's known about physiology and developmental biology.

The increased incidence of rosacea after the age of 30, and the fact that it occurs most commonly in the areas that are most exposed to sunlight (bald men sometimes develop it on the

top of the head), indicate that aging and irritation are essential causes. Stress, irritation (such as produced by ultraviolet or ionizing radiation or free radicals), and aging are known to cause disorganized growth of fibrous and vascular tissues in various parts of the body. The occurrence of these processes at the surface, where the changes can be observed immediately, and without invasive procedures, should have aroused wide interest among those who study kidney disease, diabetes, and other degenerative diseases in which fibrosis and neovascularization play important roles.

A localized stress or irritation at first produces vasodilation that increases the delivery of blood to the tissues, allowing them to compensate for the stress by producing more energy. Some of the agents that produce vasodilation also reduce oxygen consumption (nitric oxide, for example), helping to restore a normal oxygen tension to the tissue. Hypoxia itself (produced by factors other than irritation) can induce vasodilation, and if prolonged sufficiently, tends to produce neovascularization and fibrosis.

Sensitivity to the harmful effects of light can be increased by some drugs and by excess porphyrins produced in the body (and by the porphyrin precursor, delta-amino levulinic acid), leading to rosacea, so those factors should be considered, but too often alcohol (which can cause porphyrin to increase) is blamed for rosacea and rhinophyma, without justification. There are many ways in which poor health can increase light sensitivity. Some types of excitation produced by metabolites (or by the failure of inhibitory metabolites) can produce vasodilation, involving the release of nitric oxide (Cardenas, et al., 2000), setting off a series of potentially pathological reactions, including fibrosis. The nitric oxide increases glycolysis while lowering energy production. The excitatory metabolite glutamate, and nitric oxide, are both inhibited by aspirin (Moro, et al., 2000).

When blood flow in skin affected by rosacea was measured, circulation was 3 or 4 times higher than normal (Sibenge & Gawkrodger, 1992), and oxygen tension may be increased. An inability to extract oxygen from the blood, or to use it to produce energy, will produce the same hyperemia that would be produced by a lack of oxygen. These measurements suggest that mitochondrial defects would be the best place to look for a general cause of rosacea.

When mitochondria are damaged, active cells produce increased amounts of lactic acid, even in the presence of adequate oxygen. Otto Warburg identified this kind of metabolism, aerobic glycolysis, as an essential feature of cancer, and showed that it could be produced by stress, ionizing radiation, carcinogenic toxins, and even by a simple oxygen deficiency. Other investigators around the same time showed that lactic acid produces vasodilation (for example, in the cornea), and more recently it has been shown to promote the development of fibrosis, and it has been called a "phlogogen," a promoter of inflammation.

Riboflavin, vitamin B2, is an essential component of the mitochondrial respiratory enzymes, and it is very easily destroyed by light (blue light and especially ultraviolet). When it is excited by high energy light, it can spread the damage to other components of the mitochondria, including the cytochromes and the polyunsaturated fatty acids. The other B vitamins are affected when riboflavin's actions are disturbed.

Vitamin K is also extremely light sensitive, and it interacts closely with coenzyme Q in regulating mitochondrial metabolism. For example, mitochondrial Complex-I, NADH-ubiquinone reductase, is probably the most easily damaged part of the mitochondrion, and it is protected by vitamin K. Vitamin E, coenzyme Q, and the polyunsaturated fatty acids are also light sensitive, and they are more susceptible to free radical damage when vitamin K is deficient.

Niacinamide, one of the B vitamins, provides energy to this mitochondrial system. Under stress and strong excitation, cells waste niacinamide-NADH, but niacinamide itself has a sedative antiexcitatory effect, and some of its actions resemble a hormone. Estrogen tends to interfere with the formation of niacin from tryptophan. Tryptophan, rather than forming the sedative niacin (pyridine carboxylic acid), can be directed toward formation of the excitatory quinolinic acid (pyridine dicarboxylic acid) by polyunsaturated fatty acids. Excitation must be in balance with a cell's energetic resources, and niacinamide can play multiple protective roles, decreasing

excitation, increasing energy production, and stabilizing repair systems. The state of excitation and type of energy metabolism are crucial factors in governing cell functions and survival.

The polyunsaturated fatty acids, besides their interactions with estrogen and tryptophan metabolism, promote excitation and decrease energy production in several other ways. For example, they increase the excitatory effects of the glutamate pathways (Yu, et al., 1986; Nishikawa, 1994), and their breakdown products inhibit mitochondrial respiration (Humphries, et al., 1998; Picklo, et al., 1999; Lovell, et al., 2000).

The excess excitation that produces nitric oxide and lactic acid lowers the energy production of vascular cells, possibly enough to lower their contractile ability (Geng, et al., 1992), causing vasodilation. When flushing is caused by a mismatch between energy supply and energy demand, caffeine can decrease the vasodilation (Eikvar & Kirkebøen, 1998), but when vasodilation is caused more physiologically by carbon dioxide, caffeine doesn't have that effect (Meno, et al., 2005). In a study in which drinking hot water or coffee was compared with drinking room-temperature coffee or caffeine, it was found that the hot liquids caused flushing, but cool coffee and caffeine didn't.

Caffeine increases cells' energy efficiency, and by opposing the effects of adenosine (secreted by cells that are stressed and energy-depleted), it can inhibit vasodilation, angioneogenesis (Merighi, et al., 2007; Ryzhov, et al., 2007), and fibrosis (Chan, et al., 2006).

One nearly ubiquitous source of inappropriate excitation and energy depletion is the endotoxin, bacterial lipopolysaccharides absorbed from the intestine (Wang and White, 1999). That this ubiquitous toxin has a role in rosacea is suggested by the observation that intestinal stimulation, to speed transit through the bowel, immediately relieved symptoms (Kendall, 2002). Increased cortisol (Simon, et al., 1998) and sepsis (Levy, 2007) interfere with mitochondrial energy production.

Simple nervous blushing or flushing is usually considered harmless, and when a person is overheated, the reddening of the skin has the function of facilitating heat loss, to restore a normal temperature. But even nerve-regulated flushing can involve a distinct interference with mitochondrial respiration, and can stimulate the overgrowth of blood vessels.

Cancer's respiratory defect that Warburg identified, fermentation with lactic acid production even in the presence of adequate oxygen, was the result of some kind of injury to the mitochondria. He showed that one of the injuries that could produce aerobic glycolysis was a deficiency of riboflavin. He observed that tumors generally were anoxic, and that cancers typically appeared in the midst of tissue that was atrophying, and suggested that the cancer cells' survival was favored by their ability to live without oxygen. This may be relevant to the observations of many surgeons of a small cancer embedded in the fibrous tissue of large rhinophymas that have been removed.

The relatively high incidence of rosacea among women (some studies indicate that it may be 3 times as common in women as in men) isn't likely to be the result of greater sun exposure, so it's reasonable to look for hormonal causes.

In old age, it's well recognized that men's estrogen level rises. But the estrogen industry has convinced women that their estrogen declines as they get older. It's common knowledge that aging rodents often go into "persistent estrus," and that their estrogen levels generally increase with age (Parkening, et al., 1978; Anisimov and Okulov, 1981). Several studies in women have shown that serum estrogen levels rise from the teens into the 40s (Musey, et al., 1987; Wilshire, et al., 1995; Santoro, et al., 1996).

Other studies show that serum and tissue estrogen concentrations are not concordant, and that some tissues may contain several times as much estrogen as the serum (Jefcoate, et al., 2001). Local irritation increases tissue estrogen content.

The antiestrogens, especially progesterone, begin declining in the 30s, so that the rising estrogen has more effect on the tissues during those years. These are the years in which the incidence of rosacea rises suddenly. Rosacea develops later on average in men, whose estrogen levels rise significantly at later ages.

Estrogen's most immediate effect on cells is to alter their oxidative metabolism. It promotes the formation of lactic acid. In the long run, it increases the nutritional requirements for the B vitamins, as well as for other vitamins. It also increases the formation of aminolevulinic acid, a precursor of porphyrin, and increases the risk of excess porphyrin increasing light sensitivity. Both aminolevulinic acid and excess porphyrins are toxic to mitochondria, apart from their photosensitizing actions. Nitric oxide, glutamate, and cortisol all tend to be increased by estrogen.

Veins and capillaries are highly sensitive to estrogen, and women are more likely than men to have varicose veins, spider veins, leaky capillaries, and other vascular problems besides rosacea. Estrogen can promote angioneogenesis by a variety of mechanisms, including nitric oxide (Johnson, et al., 2006). "Estrogens potentiate corticosteroid effects on the skin such as striae, telangiectasiae, and rosacea dermatitis" (Zaun, 1981). Early forms of oral contraceptives, high in estrogen, were found to increase acne rosacea more than three-fold (Prenen & Ledoux-Corbusier, 1971).

Lactic acid, produced under the influence of estrogen, nitric oxide, or other problems of energy formation, besides causing vasodilation, also stimulates the growth of fibroblasts. Oxygen deprivation, or damage to mitochondria, will increase lactic acid formation, and so it will immediately cause vasodilation, and if the problem is prolonged, new blood vessels will grow, and fibrous connective tissue will increase. Estrogen stimulates collagen synthesis, and it has been associated with a variety of inflammatory and fibrotic conditions (for example, Cutolo, et al., 2003. Payne, et al., 2006, suggest the use of the anti-estrogen, tamoxifen, to treat rhinophyma.)

The cornea normally contains more riboflavin even than the retina, which has a much higher rate of metabolism. When the cornea isn't able to get enough oxygen from the air for its needs (and if riboflavin is deficient, its need for oxygen is increased), surrounding blood vessels at first dilate in response to the diffusing lactic acid, to increase the blood supply to the edges of the cornea. If the problem is prolonged, the conjuctiva becomes chronically blood-shot, hyperemic, and larger more visible blood vessels grow, surrounding the cornea, or even invading the cornea. Many people, especially women, experienced problems of this sort from wearing contact lenses, especially when the lenses were made of materials very impermeable to oxygen (Dumbleton, et al., 2006).

Sunlight, and mechanical obstruction of the cornea, produce very localized effects, but those local effects are more likely to be harmful when there is a systemic nutritional deficiency or excess of estrogen. When the systemic problem is very severe, the cheeks, nose, and eyes might not be the first tissues to experience a functional disturbance.

The mitochondrial inhibition produced by the action of the parasympathetic nervous system (occurring in simple blushing) can occur wherever those nerves act, and blood vessels in all parts of the body are responsive to the acetylcholine secreted by those nerves. Sleep typically involves a shift of dominance in the autonomic nervous system toward the parasympathetic nerves, with vasodilation. Nosebleeds, especially in children, commonly occur during sleep (Jarjour & Jarjour, 2005: high incidence in sleep, and association with migraine).

A 3 year-old child who had been having an average of 2 nosebleeds every day, during a nap and at night, for several months, also had an extreme behavior problem. He became angry and sometimes violent when he went a little longer than normal between meals. After an oral dose of about ten milligrams of riboflavin, he was able to sleep without having another recurrence of the nosebleeds, and his tantrums became rare. Apparently, the nerve-regulated vasodilation produced by sleep, combined with a riboflavin deficiency, had been enough to produce nosebleeds. The energy deficit resulting from a systemic riboflavin deficiency had probably been causing him to be abnormally sensitive to glycogen depletion, producing sudden anger. In another individual, the energy problem might have taken the form of a memory problem, or of a hemorrhage in the brain or other essential organ.

A 37 year old slightly alcoholic man with a bright red nose and cheeks was an amateur fiction writer, but he was having trouble with his memory for words, and for everyday events. Even

conversationally, he had to struggle for relatively familiar words. On the suggestion that riboflavin might help his memory, by allowing his brain cells to use oxygen more efficiently, he had his doctor give him an intravenous injection of B vitamins. When I saw him the next day, his conversation was perfectly fluent, and he obviously had easy access to a good vocabulary. Just as noticeable was the normal color of his nose and cheeks. For a week, he had a daily injection of the B vitamins, and his nose color and vocabulary stayed normal. But on the weekend, after not having the shots for two days, his nose and cheeks were again maraschino cherry red, and his speech was halting, as he struggled for words. He forgot the whole episode, and neglected to return to the doctor for more of the vitamin injections. Ten years later, he had developed a medium-sized potato nose, and had his heart valves replaced.

His vitamin requirements were apparently abnormally high. At first, the problems resulting from damaged mitochondria seem mostly functional (flushing, mood, memory problems, etc.) and variable, but chronically disturbed functions lead to structural, anatomical changes, as prolonged stimulation alters tissue maintenance and growth.

Abram Hoffer, who had been treating schizophrenia and senile dementia with niacin, accidentally discovered that it cured his bleeding gums. That led to its use to treat heart disease.

The "orthomolecular" ideas of Hoffer and Linus Pauling were developed in a context of biochemistry governed by genetics, molecular biology, in which the goal was to provide a chemical that was lacking because of a genetic defect in metabolism. Their idea of using nutrients as drugs has led to many unphysiological practices, in which an isolated nutrient is supposed to have a drug-like action, and if in isolation it doesn't act like a drug, then it should be used only according to the normal genetically determined nutritional requirement.

But in reality, nutritional requirements are strongly influenced by history and present circumstances. For example, when corneal mitochondria have been damaged by riboflavin deficiency, they have been found to subsequently require more than the normal amount of the vitamin to function properly. And the presence of a certain amount of one nutrient often increases or decreases the amount of other nutrients needed.

When the interactions among energy expenditure and energy production, and cellular activation and cellular inhibition, are taken into account, then it's clear that any particular problem is likely to have many causes and many factors that could contribute to a cure.

Lactate, glutamate, ammonium, nitric oxide, quinolinate, estrogen, histamine, aminolevulinate, porphyrin, ultraviolet light, polyunsaturated fatty acids and endotoxin contribute to excitatory and excitotoxic processes, vasodilation, angioneogenesis, and fibrosis.

Carbon dioxide, glycine, GABA, saturated fatty acids (for example, Nanji, et al., 1997), vitamin K, coenzyme Q10, niacinamide, magnesium, red light, thyroid hormone, progesterone, testosterone, and pregnenolone are factors that can be increased to protect against inappropriate cellular excitation.

All of the nutritional factors that participate in mitochondrial respiration contribute to maintaining a balance between excessive excitation and protective inhibition. Riboflavin, coenzyme Q10, vitamin K, niacinamide, thiamine, and selenium are the nutrients that most directly relate to mitochondrial energy production.

Coffee is often avoided by people with rosacea, but it is a very good source of niacin and magnesium, and caffeine has some of the same cell-protective functions as niacinamide.

People suffering from rosacea have been found to be more likely than average to have suffered from styes in childhood, to have varicose veins and spider veins, and to suffer from migraines and depression.

Hypothyroidism has been identified as a factor in all of those. Good thyroid function is necessary for resistance to bacterial infection, for regulation of blood sugar, neurotransmitters, and hormones related to mood, and for the formation of progesterone. Progesterone regulates smooth muscle tone, including the walls of veins, so that a deficiency allows veins to enlarge. It also prevents overgrowth of fibrotic tissue, and in some contexts may inhibit angioneogenesis.

GABA itself tends to raise body temperature (Ishiwata, et al., 2005), by controlling vasodilation, and the factors such as progesterone which protect mitochondrial energy production are also thermogenic, supporting the GABA system. Flushing, both by directly causing heat loss and by reducing mitochondrial energy production, tends to lower body temperature.

The sun-damaged areas in rosacea can be directly provided with some of the protective factors by applying them topically. In the same way that topical lactate can cause vasodilation and disturbed energy metabolism (Rendl, et al., 2001), topical niacinamide, progesterone, vitamin K, and coenzyme Q10 can improve the metabolism and function of the local tissues. Riboflavin can probably be useful when applied topically, but because of its extreme sensitivity to light, it should usually be used only internally, unless the treated skin is covered to prevent exposure to light. Topically applied caffeine, even after sun exposure, can reduce local tissue damage (Koo, et al., 2007). Aspirin and saturated fats can also be protective when applied topically.

Some of the benefit from antibiotics probably results from the reduced endotoxin stress when intestinal bacteria are suppressed. However, antibiotics can kill the intestinal bacteria that produce vitamin K, so it's important to include that in the diet when antibiotics are used.

Some fibers, such as raw carrots, that are effective for lowering endotoxin absorption also contain natural antibiotics, so regular use of carrots should be balanced by occasional supplementation with vitamin K, or by occasionally eating liver or broccoli.

Abram Hoffer's research was instrumental in getting niacin recognized as a heart protective drug, but nearly everyone who prescribes it does so to lower blood lipids. That wasn't Hoffer's understanding of its function. He thought it acted directly on blood vessels to protect their integrity. During his studies of its effects on heart disease, he saw that it also lowered cancer mortality, and so began treating cancer patients with it, with considerable success, but there was no medical cliché that could allow the profession to follow in that direction.

The arguments I have outlined for considering rosacea to be essentially a problem of metabolic energy, and the mechanisms that I mention for restoring mitochondrial functions, might seem more complex than Hoffer's orthomolecular views. However, this approach is actually much simpler conceptually than any of the ideologies of drug treatment. It simply points out that certain excitatory factors can interfere with energy production, and that there are opposing "inhibitory" factors that can restore energy efficiency. Sometimes, using just one or two of the factors can be curative.

Because mitochondrial respiration is very similar in every kind of tissue, a physiological view of rosacea could incline us toward considering the effects of these metabolic factors in other organs during stress and aging--what would the analogous condition of rosacea and rhinophyma be in the brain, heart, liver, or kidney?

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cornea and the lens cortex and nucleus. The relative contribution of riboflavin, FMN, and FAD to the total flavin pool was markedly different in the various tissues of the eye. The proportion of tissue flavins present as riboflavin decreased from anterior to posterior. It was highest in the cornea followed by lens and retina. The pattern of distribution for FMN was: cornea greater than retina greater than lens cortex and nucleus.

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was associated with an inhibition of complex I (NADH: ubiquinone oxidoreductase) and complex II (succinate: ubiquinone oxidoreductase) activities of the mitochondrial respiratory chain, suggesting that NO blocks mitochondrial respiration in these cells. Lactate accumulated in the media of the cells, implying an increased anaerobic glycolysis, but there was no reduction of viability. An NO-dependent inhibition of mitochondrial respiration and a switch to anaerobic glycolysis would reduce energy production of the SMCs. This would in turn reduce the contractile capacity of the cell and might represent another NO-dependent vasodilatory mechanism."

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Ray Peat's Newsletter

Beware the barrenness of a busy life. **Socrates**

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Milk in context: allergies, ecology, and some myths

Food allergies are becoming much more common in recent decades, especially in industrialized countries. Most attention has been given to theories about changes in people, such as the reduction in infectious diseases and parasites, or vitamin D deficiency, or harmful effects from vaccinations, and little attention has been given to degradation of the food supply.

Our food cultures, like linguistic and moral cultures, give us some assumptions or theories about the way the world should be, and if these beliefs aren't questioned and tested, they can permeate the culture of science, turning the research process into a rationalization of accepted opinions.

In general, those who pay for research are those with an investment in or commitment to the preservation and expansion of the existing systems of production and distribution. Cheap mass production, durability and long shelf-life are more important than the effects of foods on health. The biggest industries are usually able to keep public attention away from the harm they do.

The historical economic importance of cereals and beans is reflected in the nutritional and biochemical research literature, which has paid relatively little attention to basic questions about human adaptation to the ecosystems. From the early petrochemical "Green Revolution" to the contemporary imposition of genetically altered seeds, the accumulated economic power of the food industry has taken control of the food culture.

In evaluating each research publication relating to nutrition and health, we should ask what alternative possibilities are being neglected, for "practical" reasons, cultural preferences, and business interests.

Some people with an ecological concern have argued that grains and beans can most economically provide the proteins and calories that people need, but good nutrition involves much more than the essential nutrients.

"Efficient" industrial agriculture has been concerned with cheaply producing those important nutrients, and their critics have focussed on their use of toxic chemicals, on the social damage they produce, the degradation of the soil, the toxic effects of genetic modification, their unsustainable use of petroleum, and occasionally on the lower nutritional value of chemically stimulated crops.

I think far too little attention is being given to the effects of abnormal and stressful growth conditions on the plants' natural defense systems. Plants normally synthesize some toxins and inhibitors of digestive enzymes to discourage attacks by bacteria, fungi, insects, and other predators. When a plant is injured or otherwise stressed, it produces more of the defensive substances, and very often they communicate their stress to other plants, and the resulting physiological changes can cause changes in seeds that affect the resistance of the progeny. (Agrawal, 2001)

One of many substances produced by plants in response to injury is chitinase, an enzyme that breaks down chitin, a polysaccharide that is a structural component of fungi and insects. Chitinase, which is produced by bacteria and humans, as well as by plants and other organisms, is involved in developmental processes as well as in the innate immune system. In plants, the enzyme is induced by ethylene and salicylate, in animals by estrogen, light damage, and infections, and can be demonstrated in polyps and cancers.

The two main classes of plant allergens are the stress-induced chitinases, and seed storage proteins, such as gluten. The chitinase allergens are responsible for reactions to latex (which is secreted by rubber trees in reaction to a wound), bananas, avocados, many other fruits and vegetables, and some types of wood and other plant materials. Intensive agricultural methods are increasing the formation of the defensive chemicals, and the industrialized crops are responsible for the great majority of the new allergies that have appeared in the last 30 years.

The presence of the chitinase family of proteins in humans was first discovered in the inflamed asthmatic lung. It was then found at high levels in the uterine endometrium at the time of implantation of the embryo (an inflammation-like situation) and in the uterus during premature labor. Since estrogen treatment is known to increase the incidence of asthma and other inflammations, the appearance of chitinase also in the uterus in estrogen dominated conditions is interesting, especially when the role of estrogen in celiac disease (in effect an allergy to gluten) is considered. Celiac disease is more prevalent among females, and it involves the immunological cross-reaction to an antigen in the estrogen-regulated transglutaminase enzyme and the gluten protein. The (calcium-regulated) transglutaminase enzyme is involved in the cross-linking of proteins in keratinized cells, in fibrotic processes in the liver, and in cancer. (People with celiac disease often suffer from osteoporosis and urinary stone deposition, showing a general problem with calcium regulation.)

This means that estrogen and stress cause the appearance of antigens in the human or animal tissues that are essentially the same as the stress-induced and defensive proteins in plant tissues. A crocodile might experience the same sort of allergic reaction when eating estrogen-treated women and when eating commercial bananas.

The various states of the innate immune system have been neglected by immunologists, for example in relation to organ transplantation. The "major histocompatibility" antigens are matched, but organ transplants still sometimes fail. A study found that the livers from young men had a high survival rate when transplanted into either men or women, but the livers of older women donors were rejected at a high rate when transplanted into either men or women. Exposure to estrogen increases intracellular calcium and the unsaturation of fatty acids in tissue lipids, and the expression of enzymes such as chitinase and transglutaminase, and the various enzymes in the structure-sensitive estrogen-controlled metabolic pathways.

Estrogen's actions are closely and pervasively involved with the regulation of calcium, and these changes affect the basic tissue structures and processes that constitute the innate immune system. Estrogen's effect in increasing susceptibility to "autoimmune" diseases hasn't yet been recognized by mainstream medicine.

The chemist Norman Pirie argued convincingly that leaf protein had much higher nutritional value than grain and bean proteins, and that it had the potential to be much more efficient economically, if it could be separated from the less desirable components of leaves.

The amino acid composition and nutritional value of leaf protein is similar to milk protein, which is understandable since cows produce milk from the amino acids produced in their rumens by bacteria digesting the leaves the cows have eaten. The bacteria perform the refining processes that Pirie believed could be done technologically, and they also degrade or detoxify the major toxins and allergens.

The nutrients produced in the cow's rumen are selectively absorbed into the cow's bloodstream, where the liver can further filter out any toxins before the amino acids and other nutrients are absorbed by the udder to be synthesized into milk. If cows are fed extremely bad diets, for example with a very large amount of grain, the filtering process is less perfect, and some allergens can reach the milk, but since sick cows are less profitable than healthy cows, dairies usually feed their cows fairly well.

In a recent study of 69,796 hospitalized newborns, a diagnosis of cow's milk allergy was made in 0.21% of them. Among those whose birthweight had been less than a kilogram, 0.35%

of them were diagnosed with the milk allergy. Gastrointestinal symptoms were the main reason for the diagnosis, but a challenge test to confirm the diagnosis was used in only 15% of the participating hospitals, and a lymphocyte stimulation test was used in only 5.5% of them (Miyazawa, et al., 2009). There are many publications about milk allergies, but they generally involve a small group of patients, and the tests they use are rarely evaluated on healthy control subjects.

Several surveys have found that of children who have a diagnosed milk allergy, about 2/3 of them grow out of the allergy.

People who have told me that they have had digestive problems with milk have sometimes found that a different brand of milk doesn't cause any problem.

Milk with reduced fat content is required by US law to have vitamins D and A added. The vehicle used in the vitamin preparation, and the industrial contaminants in the "pure" vitamins themselves, are possible sources of allergens in commercial milk, so whole milk is the most likely to be free of allergens.

A thickening agent commonly used in milk products, carrageenan, is a powerful allergen that can cause a "pseudo-latex allergy" (Tarlo, et al., 1995). It is a sulfated polysaccharide, structurally similar to heparin. There are good reasons to think that its toxic effects are the result of disturbance of calcium metabolism (see for example Abdullahi, et al., 1975; Halici, et al., 2008; Janaswamy and Chandrasekaran, 2008).

Besides the idea of milk allergy, the most common reason for avoiding milk is the belief that the genes of some ethnic groups cause them to lack the enzyme, lactase, needed to digest milk sugar, lactose, and that this causes lactose intolerance, resulting in gas or diarrhea when milk is consumed. Tests have been reported in which a glass of milk will cause the lactase deficient people to have abdominal pain. However, when intolerant people have been tested, using milk without lactose for comparison, there were no differences between those receiving milk with lactose or without it. The "intolerant" people consistently tolerate having a glass with each meal.

When a group of lactase deficient people have been given some milk every day for a few weeks, they have adapted, for example with tests showing that much less hydrogen gas was produced from lactose by intestinal bacteria after they had adapted (Pribila, et al., 2000).

Bacterial overgrowth in the small intestine can be caused by hypothyroidism (Lauritano, et al., 2007), and the substances produced by these bacteria can damage the lining of the small intestine, causing the loss of lactase enzymes (Walshe, et al., 1990).

Another hormonal condition that probably contributes to lactase deficiency is progesterone deficiency, since a synthetic progestin has been found to increase the enzyme (Nagpaul, et al., 1990). The particular progestin they used lacks many of progesterone's effects, but it does protect against some kinds of stress, including high estrogen and cortisol. This suggests that stress, with its increased ratio of estrogen and cortisol to progesterone, might commonly cause the enzyme to decrease.

Two other ideas that sometimes cause people to avoid drinking milk and eating cheese are that they are "fattening foods," and that the high calcium content could contribute to hardening of the arteries.

When I traveled around Europe in 1968, I noticed that milk and cheese were hard to find in the Slavic countries, and that many people were fat. When I crossed from Russia into Finland, I noticed there were many stores selling a variety of cheeses, and the people were generally slender. When I lived in Mexico in the 1960s, good milk was hard to find in the cities and towns, and most women had fat hips and short legs. Twenty years later, when good milk was available in all the cites, there were many more slender women, and the young people on average had much longer legs. The changes I noticed there reminded me of the differences I had seen between Moscow and Helsinki, and I suspect that the differences in calcium intake were partly responsible for the changes of physique.

In recent years there have been studies showing that regular milk drinkers are less fat than people who don't drink it. Although the high

quality protein and saturated fat undoubtedly contribute to milk's anti-obesity effect, the high calcium content is probably the main factor.

The parathyroid hormone (PTH) is an important regulator of calcium metabolism. If dietary calcium isn't sufficient, causing blood calcium to decrease, the PTH increases, and removes calcium from bones to maintain a normal amount in the blood. PTH has many other effects, contributing to inflammation, calcification of soft tissues, and decreased respiratory energy production.

When there is adequate calcium, vitamin D, and magnesium in the diet, PTH is kept to a minimum. When PTH is kept low, cells increase their formation of the uncoupling proteins, that cause mitochondria to use energy at a higher rate, and this is associated with decreased activity of the fatty acid synthase enzymes.

These changes are clearly related to the anti-obesity effect of calcium, but those enzymes are important for many other problems.

The "metabolic syndrome," that involves diabetes, hypertension, and obesity, is associated with high PTH (Ahlström, et al., 2009; Hjelmesaeth, et al., 2009).

Alzheimer's disease involves decreased mitochondrial activity and low levels of the uncoupling proteins. There is evidence that milk drinkers are protected against dementia (Yamada, et al., 2003). Cancer involves increased activity of the fatty acid synthase enzymes. Increased calcium consumption beneficially affects both sets of enzymes, uncoupling proteins and fatty acid synthase.

Multiple sclerosis relapses consistently occur at times of high PTH, and remissions consistently occur at times of low PTH (Soilu-Hänninen, et al., 3008). PTH increases the activity of nitric oxide synthase, and nitric oxide is a factor in the vascular leakiness that is so important in MS.

There are components of milk that might protect against tooth decay by inhibiting the binding of bacteria to teeth (Danielsson, et al., 2009).

David McCarron has published a large amount of evidence showing how calcium deficiency contributes to high blood pressure. The chronic elevation of PTH caused by calcium deficiency causes the heart and blood vessels to retain calcium, making them unable to relax fully.

Intravenous infusion of calcium can relax blood vessels and improve heart function. The suppression of PTH is probably the main mechanism.

PTH (like estrogen) causes mast cells to release promoters of inflammation, including histamine and serotonin. Serotonin and nitric oxide contribute to increasing PTH secretion.

Removal of the parathyroid gland has reduced heart problems and mortality (Costa-Hong, et al., 2007) and insomnia (Esposito, et al., 2008; Sabbatini, et al., 2002) in people with kidney disease and excess PTH.

Increased carbon dioxide, for example when adapted to high altitude, can greatly decrease PTH. Frequent, but smaller, meals can reduce PTH.

Cancer cells often secrete PTH and related proteins with similar effects on calcium, and the PTH stimulates the growth and invasiveness of prostate cancer (DaSilva, et al., 2009) cells, and seems to be as closely involved with breast cancer. The PTH-related protein is associated with calcification in breast cancer (Kanbara, et al., 1994). Microscopic calcium crystals themselve produce inflammation (Denko and Whitehouse, 1976).

Besides being an ecologically favorable source of calcium, protein, sugar, and fat, the composition of milk causes it to be digested efficiently, supporting the growth of bacteria that are relatively safe for the intestine and liver, and reducing the absorption of endotoxin.

Dividing any food into smaller meals can lower the PTH, and milk is a convenient food to use in small amounts and frequently.

Some amino acids directly stimulate insulin secretion, decreasing blood sugar and leading to the secretion of cortisol in reaction to the depression of blood glucose. The presence of lactose in milk, and of fat, to slow absorption of the amino acids, helps to minimize the secretion of cortisol. The main protein of milk, casein, seems to have some direct antistress effects (Biswas, et al., 2003).

Since milk's primary biological function is to support the growth of a young animal, some of its features make it inappropriate as a sole food for an adult. To support cell division and growth, the methionine and tryptophan content of milk is higher than would be optimal for an adult animal, and the phosphate might be slightly more than needed, in relation to the calcium. Since the fetus stores a large amount of iron during gestation, the iron content of milk is low, and when a young animal has used the stored iron, its continuing growth requires more iron than milk provides. However, for an adult, the low iron content of milk and cheese makes these foods useful for preventing the iron overload that often contributes to the degenerative diseases.

Combining milk and cheese with fruits adds to the antistress effect. The additional sugar and potassium and other minerals allow the milk protein to be used more efficiently, by moderating the secretion of cortisol, and helping to inhibit the secretion of PTH.

Substances such as PTH, nitric oxide, serotonin, cortisol, aldosterone, estrogen, thyroid stimulating hormone, and prolactin have regulatory and adaptive functions that are essential, but that ideally should act only intermittently, producing changes that are needed momentarily. When the environment is too stressful, or when nutrition isn't adequate, the organism may be unable to mobilize the opposing and complementary substances to stop their actions. In those situations, it can be therapeutic to use some of the nutrients as supplements. Calcium carbonate (eggshell or oyster shell, for example) and vitamins D and K, can sometimes produce quick antistress effects, alleviating insomnia, hypertension, edema, inflammations and allergies, etc., but the regular use of milk and cheese can prevent

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Ray Peat's Newsletter

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To the wicked, everything serves as pretext. – Voltaire

Inflammation, endotoxin, estrogen, and other problems

Over the last few decades, the meaning of inflammation has changed a little, from being thought of simply as an essential part of the immune reaction, to being recognized as something that can interfere with the immune system, and that contributes to chronic disease and degeneration.

Many components of the inflammatory reaction have been identified lately, but the way those fit into the context of the whole organism still isn't clear.

Many of the "evolutionary interpretations" of particular biological features are just words, empty speculations that can't be tested. (Selective breeding experiments and comparative physiology can provide some basis for arguments about the evolution of the immune system, but the people who created the "big picture" weren't burdened by a need for detailed evidence.)

Developmental processes, however, have been studied in great detail, and as information accumulates, it is becoming clear that the traditional view of inflammation has little to do with reality. When inflammation is "explained" as something that evolved to protect the organism against infection, people will be taught that theory, and will feel no need to think about the subject again.

With the newer realization that inflammation can lead to cancer, heart disease, diabetes, dementia, and other degenerative processes, the logical seeming course of action for people taught the traditional "evolutionary" view of inflammation has been to look for the infectious organism causing the problem.

But if we put inflammation into the developmental context, it is immediately clear that infectious agents are just one of the many factors that we interact with and that can be involved in the inflammatory and degenerative processes. Nutrition, toxins, environmental stresses, and biological cycles influence the way we react to infectious organisms, and even in the absence of virulent organisms, can cause inflammation and degeneration. In the uterus and ovary, for example, inflammatory and degenerative changes are part of normal functioning.

In those organs, the cyclic changes in structure are orchestrated to a monthly rhythm that makes them very obvious. But in other organs, such as the adrenal cortex, the intestinal epithelium, the liver, and the skin, there is a continuous process of renewal (and degeneration) of cells that is fairly well known, despite the dogmatists who want to cling to the "Hayflick limit," that denies the existence of a flowing renewal of cells in every organ, or that insists that no renewal is possible after 50 divisions of a cell line. Cell renewal occurs even in the brain and the heart. The Hayflick doctrine was plausible to people who were committed to a Weismannist view of genetics and development, a view that radically denied the role of organismic and environmental interactions in development.

Cells that are well insulated from the environment can live for a very long time, but cells that directly contact the environment, i.e., the skin and the intestinal epithelium, divide rapidly, and are shed.

When stimulation is great, and energy supply is weak, a cell will either adapt to the conditions, sometimes increasing its rate of division, or die. Nerve cells can protect themselves by becoming insensitive to stimulation; in some cases, the

stress-induced loss of its axon can probably turn a nerve cell into a resting, or stem, cell.

The dissolution of a cell releases its materials in different ways, according to the conditions that caused it to die. Sometimes it releases histamine and other substances that can increase blood flow in nearby capillaries, but under other conditions it can liquefy without causing much change in its environment. When a significant amount of cellular debris accumulates in an area, wandering cells sense it, and depending on the nature of the injury, they may simply remove the debris, or stay and adapt, forming part of a repair structure.

Proteolytic enzymes and nucleases can decompose most of the structural proteins and nucleic acids, but the lipases that act on the dead cell's structural lipids release a variety of modified phospholipids, fatty acids, and cholesterol, with considerable biological activity or significance. These substances appear with regularity when cells are being damaged, and they are the most important class of signals acting on the immune system. Oxidized phospholipids can cause other cells to form a variety of substances that amplify the alarm signal (e.g., Kadl, et al., 2002). Their importance justifies the view of J. Cunliffe and P. Matzinger, that the immune system is actually a system of structural development and maintenance, and that its role in killing alien organisms is triggered when tissue damage releases our intrinsic signal substances.

Polyunsaturated fatty acids, derived from foods, have a special role in the immune system, intensifying the effects of stress (cholesterol newsletter, September, 2005) in killing lymphocytes, and blocking the proliferative response of thymic cells (Rotondo, et al., 1994). They tend to shift immune functions from cellular immunity to humoral (antibody) immunity, and this pattern predisposes to autoimmunity. They are probably directly toxic to the liver (Ritskes-Hoitinga, 1998). DHA increases the leakiness of the bowel, allowing more endotoxin to enter the circulation (Roig-Perez, et al., 2004).

When cells have enough glucose, oxygen, and thyroid hormone, and aren't being over-stimulated, energy consumption can be uncoupled from the formation of ATP. This allows the mitochondria to devote more energy to the production of the material needed for synthesizing cholesterol and its derivatives, pregnenolone, progesterone, and DHEA, and to form carbon dioxide at a high rate. Uncoupling helps to lower the formation of inflammatory cytokines (Horvath, et al., 2003). A chronically "uncoupled" metabolic state has been associated with longevity (Speakman, et al., 2004). The rate of cholesterol production, and the amount in circulation, tend to be inversely related to systemic inflammation. All of the types of lipoprotein absorb, bind, and help to eliminate endotoxin, for example. Carbon dioxide and the major steroids stabilize cells against excessive stimulation, and protect the cell structure.

Bacteria and plants produce a variety of lipids that serve some purposes analogous to our cholesterol and phospholipids. Some of the common intestinal bacteria produce a molecule containing amino sugars and fatty acids (lipopolysaccharide, LPS), that's called endotoxin. The "endo" root distinguishes it from the "exotoxins" secreted by some bacteria, because the endotoxin is a structural part of the bacterium, that protects the bacterium against some of the exotoxins produced by other microorganisms. Normally, our intestine and liver destroy most of the LPS endotoxin before it reaches the general circulation. The bile acids, a major end product of cholesterol, have a detergent action in the intestine that usually keeps endotoxin in solution, away from the absorptive surfaces of the intestine. If the flow of bile is obstructed, endotoxin is allowed to enter the system (Bertok, 2004). Estrogen can inhibit the flow of bile (Stieger, et al., 2000). A mucus lining is part of the protective barrier, but the microscopic integrity of the intestinal cells themselves finally regulates the passage of materials into the blood and lymphatic vessels.

The barrier function of the intestine is weakened by poisons, malnutrition, and the reduced circulation that can result from stress. Estrogens, such as oral contraceptives or Premarin, can cause colitis by shutting off the blood supply (Gurbuz, et al., 1994; Deana and Dean, 1995).

When our cells are exposed to LPS, they produce many of the same reactions that they

would produce in response to our endogenous phospholipids. The major proteins that interact with cholesterol contain lipophilic regions called beta sheets, in which a relatively flat surface is formed by parallel strands of the protein. LPS contains a group of fatty acids bound together by the polysaccharide, that strongly binds to these proteins.

The alarm reaction produced either by damage of some of our own tissue or by the entrance of LPS into the circulation can, under ideal circumstances, lead to a series of protective and defensive reactions, that resolve the problem. The production of steroids is increased, and, early in life, the liberation of fatty acids itself can contribute to the antiinflammatory processes that restore the barrier function and energy production. But when the endogenous omega-9 fatty acids have been thoroughly displaced by dietary omega-6 and omega-3 fatty acids, the systemic release of fatty acids becomes an amplifier of the stress state initiated by injury or other stress. The liver, for example, decreases its detoxification of estrogen in the presence of polyunsaturated fatty acids.

In the ovary and uterus, the healthy alternation of excitation and quiescence usually continues for many years, and in rodents it often ends in a state of "persistent estrus," in which the excitatory state can't be terminated in the usual way, by the production of progesterone. In humans, menopause is analogous, because the excitatory FSH hormone from the pituitary becomes excessive, with the ovary continuing to produce estrogen but failing to produce progesterone, sometimes with the pituitary failing to shift from FSH to LH. In rodents, it's recognized that persistent estrus is caused by chronically elevated estrogen, but in humans there has been tremendous resistance to the recognition of estrogen's central role in menopause and senescence. An excess of the basic promoter of inflammation, serotonin, which is closely associated with estrogen's influence, can have similar effects on the reproductive cycle (Cooper, et al., 1986). The industry has devoted the necessary funding to making the easily manipulated medical culture, and the public, believe the opposite, i.e., that reproductive aging is mainly caused by estrogen deficiency.

The liver, besides its important role in keeping endotoxin from reaching the circulation, normally "destroys" all of the estrogen that reaches it, that is, it makes it water soluble so that it will be excreted in the urine or bile, rather than being retained by cells. But in malnutrition, hypothyroidism, or stress, the liver allows estrogen to pass through without being completely inactivated. M.S. Biskind and G.R. Biskind (1941, 1946) showed that the B vitamins were crucial for estrogen elimination, and others around the same time demonstrated that toxins, protein deficiency, hypothyroidism, and even hyperestrogenism itself tended to reduce the liver's ability to detoxify estrogen. Endotoxin's inhibition of this detoxifying system (Banhegyi, et al., 1995) is just one of the ways that it increases estrogen systemically.

Estrogen, which was named for a gadfly, is excitatory in all of its biological actions (including nervous excitation and cellular proliferation), and in most tissues this excitatory action has been shown to cause oxidation damage. Many different toxic changes have been produced in the liver by estrogen, but lipid peroxidation can be clearly demonstrated in the liver as an early reaction to subcutaneous estrogen injection (Genc, et al., 1999).

Endotoxin and estrogen interact in many interesting and potentially deadly ways. Both of them activate many of the same alarm systems, including phospholipases, nitric oxide synthase, tumor necrosis factor (TNF), interleukins (including IL-6, according to Bengtsson, et al., 2004), and the enzymes that form prostaglandins from polyunsaturated fatty acids. Estrogen makes the toxic-mediator-producing cells in the liver (Kupffer cells) hypersensitive to LPS--15 times more sensitive than normal (Ikejima, et al., 1998). One way estrogen increases the toxicity of endotoxin is probably by making the intestine more permeable (Enomoto, et al., 1999). The acute phase reaction, a process in which the liver decreases its production of albumin and increases the production of serum amyloids, lipoproteins, and fibrinogen, is promoted by both estrogen and endotoxin. Estrogen (like endotoxin) activates nuclear factor kappa-B (Shyamala and Guiot, 1992; Hamilton, et al., 2003), which activates

cells to produce TNF, nitric oxide, prostaglandins, and interleukins. A long series of observations have indicated that estrogen's main effects begin with redox changes in the mitochondria, and recent evidence (Felty and Roy, 2005) shows that oxidative free radicals produced in the mitochondria by estrogen induce NF kappa-B. Old age is associated with increased activity of NF kappa-B.

Aspirin, increased levels of carbon dioxide (Ni Chonghaile, et al., 2005), and progesterone (Deroo and Archer, 2002; Kelly, et al., 2001; Allport, et al., 2001; van der Burg and van der Saag, 1996; Caldenhoven, et al., 1995) inhibit NF kappa-B, and NF kappa-B inhibits the synthesis of both testosterone (Hong, et al., 2004) and progesterone (Allport, et al., 2001).

The amount of injury needed to increase the endotoxin in the blood can be fairly minor. Two thirds of people having a colonoscopy had a significant increase in endotoxin in their blood, and intense exercise or anxiety will increase it. Endotoxin activates the enzyme that synthesizes estrogen while it decreases the formation of androgen (Christeff, et al., 1992), and this undoubtedly is partly responsible for the large increases in estrogen in both men and women caused by trauma, sickness or excessive fatigue.

The positive interactions among estrogen and endotoxin and NF kappa-B, and their negative interactions with progesterone and testosterone, tend to "stabilize" the inflammatory condition. In a young person, good food, sunlight, and a high altitude can often overcome severe and progressive inflammatory conditions. In an older person, whose tissues contain larger amounts of polyunsaturated fats and their breakdown products, it takes more environmental support to get out of the inflammatory pattern.

Glycine (the main amino acid in gelatin) is an important nutrient with powerful antiinflammatory actions (Zhong, et al., 1999; Wang, et al., 2004). Saturated fatty acids can help to reduce chronic inflammatory states, but it's essential to eliminate as far as possible the unstable polyunsaturated fatty acids, which suppress normal immune functions, besides contributing to the free radical-lipid peroxidation burden. Cholesterol and ATP have been used therapeutically, but ordinarily their synthesis can be increased safely by using a diet that contains a significant amount of ordinary sugar (sucrose, from fruits) when the thyroid function is adequate.

Since vascular leakiness is involved in the inflammatory syndromes, as well as in shock, I think it's reasonable to treat them similarly, keeping in mind the importance of normal blood volume and viscosity. Sodium and sugar help to lower adrenaline, and so they can make a contribution to preventing high blood pressure, while maintaining normal hydration of the blood. Estradiol and cholera toxin, which both increase vascular leakiness, probably exert some of their influence by lowering the osmotic tension of the extracellular fluid (Webster, et al., 1984; Witten and Bradbury, 1951). The enzyme activated by cholera toxin, estrogen, and hypotonic medium in the study by Webster, et al., was ornithine decarboxylase, which produces the polyamines. The polyamines promote cellular proliferation, and promote the actions of the excitotoxic amino acids. Histamine also activates excitotoxicity, and magnesium opposes it.

The inflammatory states that produce the age-related degenerative diseases have many things in common with "pre-eclampsia" or pregnancy toxemia, and the same simple things can usually alleviate both kinds of problem. With aging, intracellular water tends to decrease, as the extracellular water increases (Lesser and Markovsky, 1979), probably because of reduced cellular energy, and increased vascular permeability. When albumin production is adequate, it "binds" sodium, and the combination osmotically increases the ability of the blood to retain water.

Sodium bicarbonate can provide a little extra carbon dioxide, along with the sodium, and its diuretic action is well established, but it works by improving perfusion of the tissues, reducing any abnormal water retention, rather than by causing the kidneys to lose water in unphysiological ways. One of progesterone's important functions is the maintenance of blood volume, and adequate thyroid is essential for preventing hyponatremia (insufficient sodium in the blood, which often occurs in combination with decreased formation of albumin).

Stress, trauma, and shock start an inflammatory process, that can cause progressive damage to the organs, including the liver. Giving progesterone following the injury protects against the increase of TNF, IL-6, and leakage of liver enzymes (Kuebler, et al., 2003). It has similar protective effects in the brain, lungs, and other organs. During the normal menstrual cycle, IL-6 is inversely related to the level of progesterone (Angstwurm, et al., 1997).

The liver's important role in regulating endotoxin and estrogen, and the cascade of inflammatory mediators that can be released as a result of a depression of the liver's function, makes it important to keep the liver in mind, even when the immediate problem seems to be in the brain, the lungs, kidneys, pancreas, blood vessels, heart, eyes, prostate, ovaries, muscles, or any other organ.

Estrogen is obviously part of a primitive repair system, more fundamental or general than its role in reproduction. When a tissue is injured, it forms large amounts of an enzyme, beta-glucuronidase, that removes the water soluble sugar acid, glucuronic acid, from the estrogen glucuronide which circulates harmlessly in the blood after its formation in the liver, and before its elimination in the urine. The injured tissue reverses the inactivation of the estrogen that has occurred in the liver, causing the fat soluble estrogen to remain in the damaged tissue, where it changes the metabolism, activating enzymes that stimulate proliferation and accelerate collagen formation and other processes involved in repair. (Other enzymes, sulfatases and aromatase, contribute to the increase in estrogen in stressed tissues, but beta-glucuronidase has been studied most, because it is very easy to identify.)

These local processes don't depend on liver failure to become active, but in the systemic effects of liver failure they probably play a very important role in amplifying the effects of endotoxin and unprocessed estrogen.

The effects of endotoxin and estrogen on cells are additive, for example in causing vascular leakiness (e.g., Tollan, et al., 1992), even in the brain (Oztas and Kaya, 1998). Dementia, respiratory distress/shock lung, and all of the classical inflammatory conditions, are promoted by the simple process of making capillaries excessively permeable. But the cellular changes that make capillaries leaky, also affect other cells, changing their antigenicity, leading to "autoimmune" processes (Sekigawa, et al., 2004).

Protein deficiency creates an inflammatory state, and since stress causes tissue proteins to be destroyed and converted into sugars and fats, it's common to underestimate the amount of protein needed. One of the functions of sucrose in the diet is to reduce the production of cortisol, and so to spare protein.

Milk has a variety of antiinflammatory functions. Its saturated fats help to prevent oxidation of lipids, including cholesterol. Several of its vitamins, especially vitamins D and K, have antiinflammatory and even antiestrogenic actions. Since the parathyroid hormone (like some of the other pituitary hormones) is pro-inflammatory, a generous supply of calcium is important because it inhibits the secretion of the parathyroid hormone.

Stress activates the endorphin system (partly by increased histamine, according to Kjaer, et al., 1993), and these intrinsic hormones, like morphine and the other opiates, are pro-inflammatory. Both estrogen and endotoxin activate the endorphin system. Excessive exposure to estrogen destroys many of the beta-endorphin nerves in the hypothalamus, resulting in an adaptive hypersensitivity, that maintains a chronic activation of the endorphin sensitive tissues, suppressing progesterone production (Desjardins, 1995).

There are drugs (e.g., naloxone) that can help to block the actions of the endorphins, and since the endorphins inhibit the luteinizing hormone (LH) which promotes the production of progesterone and testosterone, a little naloxone can often restore normal menstrual cycles that have stopped because of stress and excessive exposure to estrogen. Endorphins are probably involved in menopausal flushing, and drugs of the naloxone type have been used to relieve it. But a combination of other antistress factors can do the same.

Salicylic acid, which occurs naturally in many fruits, as well as in aspirin, is unlike the other antiinflammatory drugs so vaguely classified with

it as "nonsteroidal," in having a broad spectrum of antiinflammatory effects, inhibiting the prostaglandins and NF kappa-B, TNF, and IL-6, besides contributing to the inhibition of estrogen synthesis and actions.

Magnesium is lost during stress, and that can lead to destabilization of the mast cells, with increased release of histamine and other promoters of inflammation and excitation. Thyroid hormone helps cells to assimilate and retain magnesium. Estrogen's effect on magnesium seems to be antagonistic (e.g., Muneyyirci-Delale, et al., 1999). Fruits and meats are good sources of magnesium, but coffee and chocolate are among the best sources of it, and the caffeine they contain adds to their antiinflammatory and liver-protective effect (see Sakamoto, et al., 1999).

The saturated fatty acids found in coconut oil inhibit the formation of histamine (Mimura, et al., 1980), as does glucose (Kaneko, et al., 1997), and prevent leakiness of the intestine, protecting the liver from endotoxin (Kono, et al., 2003). Progesterone and testosterone protect against histamine, while estrogen increases its formation and actions. Benadryl (diphenhydramine) protects the liver and other organs from various toxins, and from the toxic effects of histamine.

Thyroid's antiinflammatory function in arthritis and rheumatic conditions has been known for about a century, but there aren't many contemporary publications on its roles in inflammation and degeneration (see Bartalena, et al., 1994; Rittenhouse and Redei, 1997).

TSH, the thyroid stimulating hormone secreted by the pituitary, stimulates some of the inflammatory mediators, and although the definition of the "normal range" has been decreasing, the people I see whose TSH is "normal" aren't as healthy as those whose TSH is well "below normal." Other indicators of adequate thyroid function are needed.

Expired carbon dioxide ("end tidal") is a good indicator, but it's rarely measured. Lactic acid tends to rise in hypothyroidism, so measuring its level in the blood can be helpful. Oxygen consumption, serum cholesterol, daily cycle of temperature and pulse rate, and calorie consumption are good indicators of thyroid function. The inflammatory cytokines can activate the glycolytic enzymes that produce lactic acid (Bauer, et al., 2004), and the thyroid hormone accelerates the oxidation of lactic acid, so I think it's reasonable to think of a higher metabolic rate as a corrective compensation for inflammation, as well as the most important factor in preventing it.

Anyone can measure their calorie consumption with enough accuracy to be useful. Considering that the Criles' measurements of oxygen consumption in the 1930s showed that Americans as a group were extremely hypothyroid, and that other studies done around the same time suggested that nearly half of the population benefitted from supplemental thyroid, we should probably ignore the present "official" recommendations regarding caloric require- ments.

Besides keeping track of the caloric value of the food we eat, it's possible to estimate our metabolic rate fairly closely by measuring our daily fluid intake, and subtracting the amount of urine produced during 24 hours. The missing water was evaporated, and with moderate atmospheric humidity, we evaporate about a liter of water for every 1000 calories we burn.

One of the roles of fat in the food is to stimulate the secretion of bile by the gall bladder. Besides that important function, saturated fats have a variety of protective, antiinflammatory effects, including the reduction of endotoxemia and lipid peroxidation (Nanji, et al., 1997). "Coconut oil completely abolished the responses to endotoxin" (Wan and Grimble, 1987).

Appetizing foods stimulate the digestive secretions, but it's important to avoid foods that directly trigger an inflammatory reaction, or that are indigestible and as a result support harmful bacterial growth. Cellulose can accelerate transit through the intestine and lower estrogen systemically (partly by simply preventing the reabsorption of estrogen that has been secreted by the bile), but the lignans found in many seeds and grains tend to promote inflammation. Raw carrots, for example, lower estrogen, while flax meal can increase it.

Constipation or diarrhea, or their alternation, usually develops when there is inflammation in the bowel. A laxative can sometimes reduce the inflammation, but it's important to identify the

foods that contribute to the problem. A salad of shredded carrot, with oil and vinegar dressing, has a germicidal action, and is stimulating to the digestive processes. Most salad vegetables, though, are likely to produce intestinal irritation, directly or as a result of bacterial decomposition.

One or a few of the antiinflammatory measures can often make a tremendous difference, but for serious chronic problems, it's best to use as many safe techniques as possible, including periodic breathing in a paper bag to increase carbon dioxide retention, and taking niacinamide to inhibit lipolysis, until the signs of inflammation begin to subside. Eventually, the goal should be to become "deficient" in the "essential fatty acids," since experiments have shown that such animals are extremely resistant to endotoxin poisoning (Li, et al., 1990).

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Ray Peat's Newsletter

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Meat physiology, stress, and degenerative processes

The US Department of Agriculture claims that the Pure Food and Drugs Act of 1906 and the Meat Inspection Act of the same year were passed because the food industry demanded them. Ordinary historians believe that Upton Sinclair's 1905 serial publication of his novel about the meat industry, *The Jungle*, caused the public and Theodore Roosevelt to pressure Congress to pass the laws. Sinclair's descriptions of the use of poisonous preservatives and deodorants to disguise the smell of rotten meat angered the public and the president enough to overcome the industry pressure that had kept the US Congress from regulating the commercial food supply long after European governments had begun regulating food production and sales.

Before the government's intervention, it was common practice to soak all kinds of meat in water or chemical solutions to increase their weight. At present, the US Department of Agriculture, through the mass media and funding the training of food technologists and "meat scientists," now takes the position that it is natural for meat to leak water after it is packaged, and says it is perfectly legal for meat producers to soak the meat in water with chemicals until it has increased its weight by 8%. The chemicals, such as trisodium phosphate (in a solution strength as high as 12%), are chosen because they powerfully stimulate swelling and water retention. Considerable amounts of some chemicals, such as sodium citrate, are allowed to add to the weight of the meat. The use of ozone and hydrogen peroxide to deodorize meat causes instantaneous oxidative changes, including lipid peroxidation and protein carbonyl formation, as well as increasing water retention.

Most supermarket meat is now packaged with thick diapers so the buyer won't notice that he is paying for a sizeable amount of pink water. The USDA has an internet site, and consumer hotlines, to inform angry consumers that they are mistaken if they believe that meat shouldn't leak. They explain that meat is now "bred" to contain less fat, and so it contains more water, and that it is simply the leanness of the meat that accounts for its poor flavor.

Before the slaughtered animal is put into the soaking solution to gain a specific amount of weight, the animal has almost always been treated in ways that cause it to go to slaughter in a state of massive edema. Even before the meat is soaked, the animal has been treated to maximize its water retention.

Muscle physiologists and endocrine physiologists know that fatigue, stress and excess estrogen can cause the tissues to swell hugely, increasing their weight and water content without increasing their protein content.

As soon as cheap synthetic estrogens, such as DES, became available in the 1940s, their use in animals was promoted because it was clear that they caused massive water retention. Women who suffer from hyperestrogenism always have a problem with water retention, but they have never been known to suffer from over-developed skeletal muscles. In fact, in humans of both sexes, an excess of estrogen has been commonly associated with sarcopenia, muscular dystrophy, and atrophy of the skeletal muscles. Similar observations have been made in a variety of animals. Meat scientists are the only people I know of who have ever referred to estrogen as an anabolic steroid, in the sense of "building muscle."

When it was publicized around 1970 that DES is powerfully carcinogenic, after it had been used for several decades in the meat industry, its use was outlawed, but its illegal use continued and

was overlooked by the US government. The Swiss government has rejected meat from a large producer in Kansas because it contained DES. Other estrogens are openly used, and the US government continues to apply pressure to other countries to accept meat exports containing estrogens.

There are many ways to increase the water content of meat, besides feeding estrogen to the animal and soaking the meat after slaughter. Everything that causes water retention and tissue swelling in the living animal, that is, every kind of stress, fatigue, poisoning, malnutrition and injury, will make the animal gain weight, without consuming expensive nutritious food. Crowding, fright, and other suffering increase water retention and accelerate the breakdown of fats and proteins.

The water content of meat shouldn't be increased by any of those methods, not only because it is a form of stealing from the consumer, but because it makes the product toxic and unappetizing, and makes the production process a degrading experience.

Any chemicals, such as estrogen or arsenic, that remain in the meat are of course harmful to the consumer, but the changes they produce in the animals' tissues are the main problem. When grains and soybeans are used for fattening animals, their characteristic fatty acids are present in the meat, and are harmful to the consumer, but their complex degradation products, such as isoprene, acrolein, and isoprostanes, remain, along with the complex changes they induce in every aspect of the tissue. The reactive products of oxidative fat degradation stimulate, among other things, the adaptive/defensive production of polyamines, small molecules derived from amino acids. The polyamines, in turn, can be oxidized, producing highly toxic aldehydes, including acrolein (Sakata, et al., 2003). These molecules stimulate cell multiplication, and alter, at least temporarily, the way the cell's genes function.

An excess of water stimulates cell division, and an important mechanism in producing that effect is the increased production of polyamines by the enzyme ornithine decarboxylase. This enzyme is activated by an excess of water (hypotonicity), by estrogen, and by stress.

Besides stimulating cell division and modifying the cell's state of differentiation (including developmental imprinting), the polyamines also contribute to nerve cell excitation and excitotoxicity. Estrogen and excess water can contribute to nerve cell excitation, for example producing convulsive seizures. The polyamines are increased during seizures, and they can affect the stability of the nerve cells, for example contributing to cocaine's seizure-sensitizing action. Although they tend to block free radicals, they accelerate nerve injury (Yatin, et al., 2001), and can contribute to breakdown of the blood-brain barrier (Wengenack, et al., 2000, Koenig, et al., 1989).

The polyamines are increased in cancers, and therapies to block their formation are able to stop the growth of various cancers, including prostate, bowel, and breast cancer. Metabolites of the polyamines in the urine appear to be useful as indicators of cancer and other diseases. (In pancreatic cancer, Yamaguchi, et al., 2004; in cervical cancer, Lee, et al., 2003; in adult respiratory stress syndrome, Heffner, et al., 1995.) The quantity of polyamines in the urine of cancer patients has been reported to be 20 times higher than normal (Jiang, 1990). Polyamines in the red blood cells appear to indicate prognosis in prostate cancer (Cipolla, et al., 1990).

The polyamines in semen have been suspected to have a role in producing cervical cancer (Fernandez, et al., 1995).

In protein catabolism, one fate of the protein's nitrogen is to be converted to the polyamines, rather than to urea. In plants, at least, these small molecules help cells to balance osmotic stresses.

Adding water to meat, or stressing the animals before slaughter, will increase the meat's content of the polyamines, but the longer the meat is stored, the greater will be the production of reactive oxygen products and polyamines.

The deliberate "aging" of meat is something that the meat scientists often write about, but it has a peculiar history, and is practiced mainly in the English speaking cultures. When a supermarket in Mexico City began selling U.S.-style meat for the American colony, I got some T-bone steaks and cooked them for some of my Mexican friends. The meat wasn't water-logged (it was

1962, and the beef had been grown in Mexico), but it had been aged for the American customers, and though my friends ate the steaks for the sake of politeness, I could see that they found it difficult.

In Mexico, even in the present century, butcher shops often don't have refrigeration, and they don't need it because they sell the meat immediately. The fresh meat tastes fresh. Traditionally, liver is sold only on the day of slaughter, because its high enzyme content causes it to degrade much faster than the muscle meats. When it is fresh, it lacks the characteristic bad taste of liver in the US.

Both the liver and the muscles contain a significant amount of glycogen when they are fresh, if the animal was healthy. At first, the lack of oxygen causes the glycogen to be metabolized into lactic acid, and some fatty acids are liberated from their bound form, producing slight changes in the taste of the meat. But when the glycogen has been depleted, the anaerobic metabolism accelerates the breakdown of proteins and amino acids.

In the absence of oxygen, no carbon dioxide is produced, and the result is that the normal disposition of ammonia from amino acids as urea is blocked, and the polyamines are formed instead. The chemical names of two of the main polyamines are suggestive of the flavors that they impart to the aging meat: Cadaverine and putrescine. After two or three weeks of aging, there has been extensive breakdown of proteins and fats, with the production of very complex new mixtures of chemicals.

Mexicans, despite their low average income, have a very high per capita consumption of meat, as do several other Latin American countries. Argentina has a per capita meat consumption of nearly a pound a day. There is a lot of theorizing about the role of meat in causing cancer, for example comparing Japan's low mortality from prostate cancer, and their low meat consumption, with the high prostate cancer mortality in the US, which has a higher meat consumption. But Argentina and Mexico's prostate cancer mortality ranks very favorably with Japan's.

If meat consumption in the US contributes to the very high cancer rate, it clearly isn't the quantity of meat consumed, but rather the quality of the meat.

The polar explorer Vilhjalmur Stefansson was interested in the health effects of a diet based on meat, because of his observation that fresh meat prevented scurvy much more effectively than the fruits and vegetables carried by other polar explorers. He commented on the importance of culture and learning in shaping food preferences:

"In midwinter it occurred to me to philosophize that in our own and foreign lands taste for a mild cheese is somewhat plebeian; it is at least a semi-truth that connoisseurs like their cheeses progressively stronger. The grading applies to meats, as in England where it is common among nobility and gentry to like game and pheasant so high that the average Midwestern American or even Englishman of a lower class, would call them rotten.

"I knew of course that, while it is good form to eat decayed milk products and decayed game, it is very bad form to eat decayed fish. I knew also that the view of our populace that there are likely to be "ptomaines" in decaying fish and in the plebeian meats; but it struck me as an improbable extension of the class-consciousness that ptomaines would avoid the gentleman's food and attack that of a commoner.

"These thoughts led to a summarizing query; If it is almost a mark of social distinction to be able to eat strong cheeses with a straight face and smelly birds with relish, why is it necessarily a low taste to be fond of decaying fish? On that basis of philosophy, though with several qualms, I tried the rotten fish one day, and if memory serves, liked it better than my first taste of Camembert. During the next weeks I became fond of rotten fish."

Since Stefansson's observations nearly a century ago, most Americans have become accustomed to the taste of half-spoiled meat, as part of the process of adapting to an industrial-commercial food system. Tests done by food technologists have found that most Americans prefer the taste of synthetic strawberry flavor in ice cream to the taste of ice cream made with real

strawberries. If it took Stefansson only a few weeks to become fond of rotten fish, it isn't surprising that the public would, over a period of many decades, learn to enjoy a diet of stale foods and imitation foods.

Polyamines are increased in stressed and stored vegetables, as in aged meats. This defensive reaction retards tissue aging, and researchers are testing the application of polyamines to fruits to retard their ripening. A plastic surgeon, Vladimir Filatov, discovered that tissue stored in the cold stimulated the healing process when used for tissue reconstruction, such as corneal transplants. He found that stressed plant tissues developed the same tissue stimulants. Another pioneer of tissue transplantation, L.V. Polezhaev, saw that degenerating tissue produced factors that seem to activate stem cells.

Although the diffusion of these stimulating factors from stressed tissues normally functions to accelerate healing and tissue regeneration, under less optimal conditions they are undoubtedly important factors in tissue degeneration and tumor formation. For example, the bystander effect (contributing to delayed radiation damage, and producing a field of precancerous changes around a cancer), in which substances diffusing from injured tissues damage surrounding cells, involves disturbances in polyamine metabolism.

The direct, optimal effects of the polyamines are protective, but when excessive, prolonged, or without maintained cellular energy, they become harmful.

The expression of genes involves their physical arrangement and accessibility to enzymes and substrates. The negatively charged nucleic acids are associated with positively charge proteins, the histones. The very small positively charged polyamines can powerfully modify the interactions between histones and DNA. In recent years people have begun to speak of the "histone code," as a kind of expansion of the idea of the "genetic code." But the polyamines, produced in response to stress, might be thought of as a complex expansion of the "histone code."

The addition of small molecules, methyl and acetyl groups, to the large molecules can regulate the expression of genes, and these patterns can be passed on transgenerationally, or modified by stress. Barbara McClintock's "controlling factors" were mobile genes that caused the genome to be restructured under the influence of stress. Her discoveries were the same as those made by Trofim Lysenko decades earlier, and like his observations, McClintock's were angrily rejected until the 1980s, when the genetic engineering industry needed some scientific background and natural precedent for their unnatural intervention in the genome.

The brain is extremely different from a malignant tumor, and the derangements produced by stress, by high cortisol and estrogen and an excess of water, are different in the two types of organ (considering the tumor as an *ad hoc* organ), but the polyamines have central roles in the degenerating brain and in the divergent disorganization of tumors. Their importance in stress physiology is coming to be recognized, along with the meaning of "epigenetic development," in which the influence of the environment becomes central, rather than just a place in which the "genotype" is allowed to passively express its "genetic potential." Every developmental decision involves an evaluation of resources and their optimal marshaling for adaptation. The polyamines are part of the cytoplasm's equipment for controlling the genome. The ratio between the different types of polyamine governs the nature of their regulation of cellular functions.

The old idea, "one is what one eats," has evolved far beyond ideas of simple nutritional adequacy or deprivation, and it's now commonly accepted that many things in foods have fairly direct effects on our brain transmitters and hormones, such as serotonin, dopamine, adrenalin, endorphins, prostaglandins, and other chemicals that affect our behavior and physiology.

In 1957 James McConnell discovered that when flatworms were fed other flatworms that had been trained, their performance was improved by 50%, compared with normal flatworms. Later, similar experiments were done with rats and fish, showing that tissue extracts from trained animals modified the behavior of the untrained animals so that it approximated that of the trained animals. Georges Ungar, who did many experiments with

higher animals, demonstrated changes in brain RNA associated with learning, and he and McConnell believed that proteins and peptides were likely to be the type of substance that transmitted the learning.

A dogmatic belief that "memory molecules" would be unable to penetrate the "blood-brain barrier" allowed most biologists to dismiss their work. Ungar's death, and the hostility of most biologists to their work, have caused their ideas to be nearly forgotten for the last 30 years. Negatively charged molecules such as ordinary proteins tend to be repelled by negative charges on the wall of capillaries, but positively charged molecules spontaneously associate with cellular proteins, and easily penetrate the barrier. Highly positively charged molecules tend to concentrate in the brain (Jonkman, et al., 1983), and people are currently attempting to use the principle to deliver antibodies (which are normally excluded from the brain) therapeutically to the brain by combining them with small positively charged molecules (Herve, et al., 2001). This affinity of the brain for positively charged molecules is gradually being recognized as an important factor in the toxicity of ammonia and guanidine derivatives. As mentioned earlier, even endogenous polyamines can be involved in disruption of the blood-brain barrier.

So, apart from the question of exactly what molecules were responsible for the learning transfer produced by McConnell and Ungar, there should be no doubt that polyamines derived from food can enter tissues, especially the brain. People who eat meat from stressed animals are substantially replicating the experiments of McConnell and Ungar, except that people normally eat a variety of foods, and each type of food will have had slightly different experiences in its last days of life. But the deliberate aging of meat is subjecting it to a standardized stress--two or three weeks of cold storage. Because of the great generality of genetic processes, it wouldn't be surprising if cold storage of vegetables turned out to produce polyamine patterns similar to those of cold storage meats. Air pollution and other stressful growing conditions cause vegetables to have very high levels of polyamines.

Prolonged exposure to certain patterns of polyamines might produce particular syndromes, but the mere fact of increasing the total quantity of polyamines in our diet is likely to increase the incidence of stress-related diseases. Experiments with cells in culture show that added polyamines can produce a variety of extremely harmful changes, but so far, there has been almost no investigation of their specific regulatory functions, of their "code."

Besides rejecting stale foods produced under stressful conditions, there are probably some specific ways that we can protect ourselves from polyamine poisoning.

When the organism is functioning efficiently, its respiration is producing an abundance of carbon dioxide, which protectively modifies many systems and structures. Adequate carbon dioxide protects against fatigue, cellular and vascular leakiness, edema and swelling.

Increasing carbon dioxide will tend to direct ammonia into urea synthesis, and away from the formation of polyamines. Bicarbonate protects against many of the toxic effects of ammonia, and since carbon dioxide spontaneously reacts with amino groups, it probably helps to inactivate exogenous polyamines. This could account for some of the protective effects of carbon dioxide (or high altitude), for example its anti-seizure, anticancer, and antistress effects.

Other things that protect against excessive polyamines are procaine and other local anesthetics (Yuspa, et al., 1980), magnesium, niacin, vitamin A, aspirin, and, in some circumstances, caffeine. Since endotoxin stimulates the formation of polyamines, a diet that doesn't irritate the intestine is important. Tryptophan and methionine contribute to the formation of polyamines, so gelatin, which lacks those amino acids and is soothing to the intestine, should be a regular part of the diet.

Because the polyamines intensity the neurotoxic and carcinogenic effects of estrogen and of polyunsaturated fats, those three types of substance should be considered as a functional unit in making food choices. (Grass-fed organic beef fresh from a local farm would be a reasonable choice.) Unfortunately, the meat industry has

maximized all of those dangers, just for the increased weight of their product.

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Ray Peat's Newsletter

One thought fills immensity. ***William Blake***

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How do you know? Students, patients, and discovery

"For the real world has inexhaustible splendour, the real life is full of meaning and abundance, where we grasp it, it is full of miracles and glory." *N. Hartmann*

"I am myself plus my circumstances" *Jose Ortega y Gasset*

Knowledge should be useful and provisional.

I think comparing the doctor-patient relationship with the teacher-student relationship can be useful, and it might suggest ways that both of them could be made more productive, with implications for the nature of learning and knowing.

40 or 50 years ago, advocates of student-centered education were encouraged by the popularity of psychologist Carl Rogers' client centered therapy. Rogers was interested in what made some therapists successful, and he found that their personality and attitude, not their theories or techniques, accounted for their success. Successful therapists had three essential traits. They offered their clients acceptance or "unconditional positive regard" and empathic understanding, and they themselves were congruent, not presenting a facade of authority or esoteric knowledge. According to Rogers, "accurate diagnosis" and "specific treatment" didn't have anything to do with helping the client.

Some therapists thought Rogers' approach was impractical, others were sure it was foolish. Medically oriented psychiatrists saw Roger's prestige among psychologists as evidence that psychology wasn't suited for dealing with the "mentally ill," who needed authoritative diagnosis and treatment--such as drugs, convulsive shock, or surgery. Scientifically, however, Rogers' ideas were supported by evidence, and medical psychiatry had no evidence to support many of its diagnostic concepts or their therapeutic usefulness.

Most university professors felt that Rogers' ideas were irrelevant to their educational work, and some clearly saw their own function as being a sort of Malthusian selection of the fittest, and deliberately designed their classes as barriers that only a few could surmount.

When I taught English composition, instructors were told that they must grade according to a standard scoring system for errors of grammar, punctuation, spelling, and diction. Our success was seen in terms of the number of freshmen who had dropped out by the end of the year, as evidence that the department had "high standards." Knowing that system, most students chose to write in the style of the first grade "See Spot run" readers, hoping that they could handle the mechanics of writing if they reduced the complexity and content of their essays. It didn't work, and they didn't improve during the weeks when their mistakes were being brought painfully to their attention. Since I hated reading their meaningless efforts, I told them that I was going to grade them on content, rather than punctuation and spelling, and that they should try to write about something that was important to them. Only their success in communicating something would be graded. Their papers became more readable, and the interesting thing was that the mechanical things improved immediately. (The intention to communicate something is the real source of structure in language.) I had another teacher score some of their compositions, and he confirmed that they had improved according to the department's system. The attempt to steer a person can make it hard for them to move, because it inactivates their own guidance system.

A physics professor would notice that writing classes have a lot in common with psychotherapy,

and would dismiss the possibility that such an approach could be used in serious education.

Professors of medicine see themselves as models of the authority that their students will need to apply in dealing with patients, and the physicians trained in the authoritarian style are likely to see their patients as recipients of their medical knowledge, rather than as occasions for listening and learning something new.

Students entering these disciplines must expect to be disciplined. This means that they learn not to ask silly questions about the fundamental assumptions of their profession. Their common sense of meaning, their original guidance system, must be inactivated to keep them from asking questions such as "is that a disease or a theory?" Some patients find that their physician has little patience for their questions, but most patients don't want to ask questions, because they have been taught to respect the authorities.

Our nervous systems are made up of physiology and culture.

That can be a philosophical problem, because our experience is governed by our composition. In people like Heraclitus, physiology was in the foreground, and in people like Plato, culture was in the foreground. (Heraclitus understood that things are always becoming, Plato believed that change wasn't real.) To change someone's mind, it's necessary to change the way they experience themselves and the world, and that requires changing their substance.

In the 1950s a group called "Synectics" was formed to study the creative process. They found that having an expert in the group could be useful, but it could also often stifle the group's ability to find a good solution to a problem. W.J.J. Gordon described their method as "trusting things that are alien, and alienating things that are trusted." They used metaphorical thinking to help them to see the complexity and potentiality of a situation, and to go beyond the existing understanding.

Professors and physicians too often present themselves as having "definitive knowledge" about a subject. For people who already have "definitive knowledge" about something, anomalous facts (if they are perceived at all) will simply remain anomalous and will be quickly forgotten. The things they produce will be extensions of what already exists. For others, things that aren't easily explained have special interest, and cause them to ask new questions. New perspectives can lead to new possibilities and new realities.

Once during a lecture, Alfred Korzybski offered his students some cookies, which they seemed to enjoy, then he showed them a label on the bag, "dog cookies," and some of them felt sick. "I have just demonstrated that people don't just eat food, but also words, and that the taste of the former is often outdone by the taste of the latter." Hypnotists have often demonstrated that words can have physiological effects.

Many of our institutions use language as a system for preserving culture, that is, for preventing change. Korzybski wanted to correct the cultural habit of making abstractions seem like objects or "elements," by making people aware of the degree of abstraction in their words. This can be useful, but his book has been used to promote an extreme linguistic relativism in the theory of knowledge and science, placing "meaning" entirely within the nervous system.

This approach evades the fact that patterns exist objectively, and that they can be perceived as they unfold through time. Although Korzybski thought he was teaching people to overcome the limitations of thinking in the style of Aristotle or Plato, he was supporting an attitude that would make it impossible to perceive in the style of Heraclitus.

If Heraclitus said it's impossible to step in the same river twice, his comment was directed to those who ignore the rich complexity of experience because of stereotyped "elemental" thinking. He was pointing to the abundance of the world, but elemental-concept thinkers have felt that he simply negated their objective meanings.

To perceive another person accurately requires the ability to perceive the person as a pattern unfolding coherently through time, as a potential realizing itself. Carl Rogers' insight was that one's awareness of being perceived in this way encourages the unfolding of potentials.

The refusal of institutions or individuals to perceive others in this way is an imposition of their way of understanding, and is itself a form of oppression. People who think in terms of "professional training" often describe learning in terms of

"conditioned reflexes," producing a desired response to each stimulus.

The terms "conditioned reflex" and "conditioning" were introduced into psychology by the behaviorist J. B. Watson, who mistranslated and misrepresented Pavlov's ideas, and who insisted that the ideas of consciousness, volition, and self should be eliminated from the science of psychology.

The orienting reflex, the alertness provoked by something new, was described by Sechenov in 1863, and explored by Pavlov (who also called it the "what *is* that? reflex" and the "exploration reflex") who considered it to be our most basic and most powerful reflex. The fact that novelty powerfully arouses our exploratory systems means that we have a mental image of our familiar environment, and that a change in that environment requires us to investigate the properties of the new thing, to see whether it can be explained by the things we already know, or whether it requires us to change our basic ideas about our place in our surroundings. For Pavlov, the study of psychology or physiology without consciousness was simply crazy.

Pavlov said that he studied nutrition to understand consciousness and the nervous system, because eating is our closest interaction with the world. Our brain is part of our digestive system. But eating has become highly institutionalized and influenced by our cultural beliefs. If people begin to think about the meanings of eating, they are beginning a process of cultural and philosophical criticism.

Helping people with physical problems (such as obesity, headaches or joint or nerve pain, or named diseases) and helping people who want to understand something about the world beyond themselves, are structurally similar, but in the issues of health the questions and the potential answers are more clearly present and immediate.

The Synectics group began with the study of artistic creation, but they found that it was easier to evaluate their progress when they concentrated on technical invention. They found, as Pavlov had, that consciousness and meaning could best be studied in concrete situations. The process of goal-seeking was to be studied in action.

I see the therapeutic or educational or productive situation as a goal-directed biological and social interaction, and the goal can be either the creation of something new and better, or simply the preservation and application of something already existing.

Until just about a generation ago, "teleology" (especially in biological explanation) was considered to be metaphysical and inappropriate for science. Norbert Wiener, who coined the word "cybernetics" (from Greek for "proficient pilot" or "good steersman") helped to change attitudes toward the word when he used the phrase "teleological mechanism" to describe cybernetic control systems.

A goal-directed system is one that senses its actions and makes adaptations so that its actions can be refined to achieve a purpose. Between 1932 and 1935, a student and colleague of Pavlov's, P.K. Anokhin, developed this idea of self-regulating systems, and originated the concept of feedback, in describing the ways organisms guide themselves and their adaptations. Building on Pavlov's work, and investigating the origins of innate reflexes, he found principles that would explain the origin of organs and their functions, and that would also apply to the interactions between individuals. The functional system on any level, in embryology, psychology, or society, is a sequence of interactions with a useful result. Movement towards a goal is adaptive, and the system is shaped by the adaptations it makes in moving toward the goal. Resources are mobilized to meet needs, changing the system as it moves towards its goal.

Since there is always novelty in the real world as contexts change, the exploratory function is causing us to continually revise our understanding. Every question forms a functional system, and our brain adapts as we find answers.

This kind of systems theory and self-regulation theory developed along with the field theories in embryology, psychology, chemistry, and some branches of physics. Pattern and analogy were central to their approach. The functional systems are processes that occupy time and space.

The "field" idea in biology (wholes shaping themselves) can be understood by considering its

opposite, the belief that cells are guided by their genes (producing a mosaic of parts). That idea, in its extreme form, claimed that cells contained an internal map and an internal clock telling them when and where to move and how to change their form and function as they matured and aged. In reality, cells communicate with surrounding cells and with the material between cells. The existence of long-range ordering processes between atoms, molecules, and cells threatened some of the central dogmas of the sciences.

Although Norbert Wiener popularized some aspects of the "teleological" approach to regulatory systems in the 1950s, and saw analogies between the teleological machines and the way the brain functions in Parkinson's disease, by 1950 the digital approach to information processing, storage, and transmission was displacing analog devices in computation and engineering, and was compatible with theories of intelligence, such as neo-Kantianism, that believed that human intelligence can be defined precisely, in terms of discrete rules and operations. Field thinking in embryology, cancer theory, psychology, and other sciences effectively disappeared--or "was disappeared," for ideological reasons.

Wiener's goal-directed machines, like Anokhin's functional systems, worked in space and time, and the idea of steering or guidance assumes a context of time and space in which the adjustments or adaptations are made. Analog computers and control systems in various ways involved formal parallels with reality. The components of the system, like reality, occupied space and time.

Digital computers, with their different history and functions, for example their use for creating or breaking military codes, didn't intrinsically model reality in any way. Information had to be encoded and processed by systems of definitions. A sequence of binary digits has meaning only in terms of someone's arbitrary definitions.

Parallel with the development of electronic digital computing machines, binary digital theories of brain function were being developed, by people who subscribed to views of knowledge very different from those of Anokhin and Wiener. (Anokhin argued against the idea that nerves use a simple binary code.) These computer models of intelligence justify educational practices based on authoritative knowledge and conditioned (arbitrary) reflexes. Neo-Kantianism has been the dominant academic philosophy in the U.S., turning philosophy into epistemology to exclude ontology. "Operationism" and logical positivism share with neo-Kantianism its elimination of ontology (concern with being itself).

In the 1960s, Ludwig von Bertalanffy developed a theory of systems, defining a system as an "arrayed multitude of inter-linked elements." Although it was intended as a description of biological systems, it reduced the teleological factors, needs and goals, to a kind of mechanical inner program, such as "regulatory genes." "Following old modes of thought, some called this orderliness of life 'purposiveness' and sought for the 'purpose' of an organ or function. However, in the concept of a 'purpose' a desiring or intending of the goal always appeared to be involved--the type of idea to which the natural scientist is justly unsympathetic" (von Bertalanffy).

His system theory was highly compatible with programmed digital computers, that could define the interactions of "elements," but unlike Anokhin's definition of functional systems, it lacked a pattern-forming mechanism. In Anokhin's view, the system is formed by seeking its goal, and perceiving its progress toward the goal.

Carl Rogers' approach to person-centered processes recognized that the interacting therapist and client or teacher and student were a formative system, rather than just an occasion for one to inform the other.

In the Synectics group, they learned to identify the types of deeply involved interaction that would lead to the best inventions. As in Anokhin's functional systems, resources are mobilized or generated as they are needed. Like Anokhin, they showed that the process of creating something new can be understood and controlled.

Every meaningful interaction involves formative systems.

Stimulation of sensory nerves can cause cells to move into the stimulated area, causing the organ to grow. Environmental enrichment causes brains to become larger, and to metabolize at a

higher rate. All of these processes, from the level of energy production to the birth of new cells and the creation of new patterns in the brain, are called up in the formation of a functional system.

The studies of organismic coherence by Mae-Wan Ho and Fritz Popp appear to support the idea that even the alignment of molecules in cells is responsive to the state of the entire organism.

The reason this seems implausible to most biologists is that cells are commonly still seen as analogous to little test-tubes in which chemical processes occur as the result of random collisions between molecules floating in water. But Sidney Bernhard's study of glycolysis showed that the reactive sugar molecules are passed individually from one enzyme to the next, in an orderly manner.

In this system, the flow of energy, a series of oxidations and reductions changing glucose into other substances, effectively "pulls" the molecules through the system, contributing to order on a molecular level. Function creates structure, which supports function.

Self-regulating systems are self-ordering systems. When a person is allowed to function freely as a goal-directed, questioning system, the formation of patterns in the brain will be spontaneous and appropriate, and orderly. Knowing is the ability to hold patterns in awareness. Knowledge, rather than being stored like money in the bank, is something that is regenerated, or generated, as we need it.

When our own steering system is commandeered by the authorities, our patterns of knowledge will be compartmented, and arranged in a fixed pattern. This kind of knowledge either deteriorates, or it seeks more of its own kind.

While self-regulation and the generation of knowledge are pleasurable, having knowledge imposed isn't.

Korzybski was right in warning about the dangers of letting names become "elements." This perception led Paolo Freire to emphasize the educational importance of critically giving things their appropriate names, rather than just "banking" the names given by an authority. "To exist, humanly, is to name the world, to change it. **Once named, the world in its turn reappears to the namers as a problem and requires of them a new naming.** Human beings are not built in silence, but in word, in work, in action-reflection." ". . . to speak a true word is to transform the world." "'Problem-posing' education, responding to the essence of consciousness--intentionality--rejects communiques and embodies communication" (Freire, 1993).

Having the power to assign names is a source of power and wealth. The pharmaceutical industry has been accused of inventing new diseases to sell new drugs for treating them. Old definitions of cancer are hard to change, when the medical profession has invested so much in treatments--radiation and cytotoxic chemotherapy--which conflict with newer biological understanding of cancer.

The person who is learning is critically interacting with both nature and culture, with practical issues and theories.

Applying this to practical problems of health and nutrition, a first step is to begin to think about which things are theories or deductions from theories, which are habits, and which things are felt needs or appetites, and to get in the habit of watching processes or things--such as "signs" and "symptoms"--develop through time.

With practice, people can begin to see themselves as functional systems in their main activities, such as eating, and to watch how their needs influence their actions, and what effects different ways of eating have on their other functions, such as sleeping and working. Do appetites govern the timing of meals and the choice of foods? How does the time of day or time of month affect appetites? People often watch for effects of foods, but usually only for a few minutes or hours after eating. Some foods can produce symptoms days after they were eaten, and the activation of the digestive system by a recent meal can cause a reaction to something eaten previously.

Our traditional cultures, and advertising and schools give us definitions and expectations relating to foods and symptoms and physiology, and they teach us to think of our bodies in terms of an "immune system," "endocrine system," "digestive system," "nervous system," and "circulatory system," which are mainly anatomical concepts that are more useful to the drug companies than to

the consumer of culture. Both conventional and alternative approaches to medicine and health are likely to let those arbitrary ideas of systems cause them to overlook real, but unnamed, processes.

When the organism is seen as a mosaic of parts, rather than as a system of developing fields, medical treatments for one part, such as the "circulatory system," are likely to cause problems in other "systems," because the "parts" being treated don't exist as such in the real organism, with the result that the treatments are seldom biologically reasonable.

Besides learning to perceive one's own physiology and becoming aware of the processes of perceiving and knowing so that they can be improved, it's important to seek information to expand the interpretive framework, and to look for new contexts and implications.

Reading with a critical imagination is as important for science as it is for literature or advertising. Good literature often opens expansive new ways of seeing the world, and good science writing can do that too, but too often scientific publications have ulterior motives, and should be read the way advertising propaganda is read.

Some publications now require authors to state their conflicts of interest (such as receiving money from a drug company while testing a drug), but editors and publishers, who choose which studies will be published, seldom reveal their conflicts of interest. As Marcia Angell showed, editorial choices can turn statistical randomness into statistical significance. Private ownership of science journals permits control of their content.

Besides being aware of the conflicts of interest and the frequent insignificance of "statistical significance," it's possible to recognize some features of the style of argument which is often used in science propaganda. A deductive style, rather than a descriptive and inductive style is extremely common in technical writing, and it should always lead the reader to question the principle from which deductions are made.

"Membranes are made from Essential Fatty Acids, therefore those fatty acids are nutritionally essential." But cells can multiply in a culture medium that provides no fats. In biology, the most popular "principles" are simply dogmatic beliefs about genes and membranes.

In physics, where testable inferences can be drawn from arbitrary assumptions or doctrines, predictions that may be made based on different assumptions are often ignored for ideological reasons. This ideological quality of physics can permeate the other sciences when they use reductionist explanations.

Korzybski felt he was helping humanity to escape "word magic" and to advance to a mathematical view of the world. But the same processes that caused people to "confuse words with things" can cause people to confuse mathematical descriptions with reality.

"Chaos theory," which was a faddish excitement about the ability to generate unpredictable output from a simple rule (which could be endlessly repeated by a computer), has been suggested to explain many things in biology, including heart rate variability. It doesn't. Instead, it has probably had a slightly harmful effect, by distracting attention from real biological pattern-forming processes.

Real substance can sometimes be modeled by descriptions of randomness, but substances at all levels have intrinsic pattern-forming tendencies, and context-dependent histories. Water, for example, has structure and structural memory that can affect even simple chemical reactions, and even gases have internal complexities that are often ignored. Real observations shouldn't be dis[illegible]ed by theories. The ideal ar[illegible]tical ato[illegible] of the reductionists are a cr[illegible]asy, in[illegible], more or less consciously, [illegible]eir [illegible]al purposes. One purpose [illegible] to [illegible]eir abstract models of reality. [illegible]arly noxious way of modeling reality [illegible] been based on the assumption of randomness, justifying a statistical view of all things.

The neo-Kantian philosophy that has dominated US universities for more than a century argues that our senses (even when extended instrumentally) are limited, so our knowledge must be limited--we can only speak of theories or interpretations, not of being. The world we see is, according to them, only an artifact of our senses. A popular example is that the flower a bee sees is different from the flower a human sees, because the bee's eye is sensitive to ultraviolet light. (The triviality of the example is shown by the fact that

when a person's lens is removed because of a cataract, ultraviolet light becomes visible, because it is no longer blocked by the tissue that is many times thicker than a bee's lens.) There is a straw-man quality to their arguments against philosophical realism and empirical science: No one claims that our senses deliver complete knowledge all at once. What the realists claim is that interacting with the world is an endless source of valid knowledge.

When reading science articles, or listening to lectures, and even while privately thinking about experiences, it can be useful to watch for the improper use of assumptions. Our understanding has been shaped by the assumptions of our culture, and these assumptions present an attitude toward the nature of the world, in some cases even about the ontology that our philosophers have said is beyond our reach. "Evolution is shaped by random mutations," "nuclear decay is random," "the universe is expanding," "entropy only increases," "DNA controls inheritance," "membrane pumps keep cells alive," and all of the negative assumptions that have for so long denied the systematic generation of order.

Every communicative interaction is an opportunity for the discovery of new meanings and potentials.

Aristotelian motto: If the knower and the known form a functional system they are substantially the same.

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"...the rules of the war game never catch up with the facts of the real situation." "The future offers very little hope for those who expect that our new mechanical slaves will offer us a world in which we may rest from thinking. Help us they may, but at the cost of supreme demands upon our honesty and our intelligence." Norbert Weiner, **God and Golem, Inc.,** 1964.

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Ray Peat's Newsletter

A dry soul is wisest and best. Heraclitus

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Fatigue, Aging, and Recuperation

Old people and sick people tire easily. Surprisingly, little is known to explain that common fact.

Myths about lactic acid and oxygen debt have misdirected most fatigue research.

The cellular processes involved in fatigue overlap with those of aging.

Knowledge about the mechanisms of fatigue should be useful in preventing some tissue swelling disorders, organ failure, degenerative calcification, and other energy-related problems.

Unlike the somewhat technical medical concept of "stress," the idea of fatigue is something everyone understands, to some extent. Hans Selye's studies of stress weren't widely accepted until about 40 years after their publication, but some of the main investigators of the fatigue phenomenon are still practically unknown in the universities, many years after they published their work.

Several things have kept fatigue research from advancing, including the common feeling that fatigue is already sufficiently understood, and that it is somehow trivial, compared to problems such as growth, reproduction, and disease.

Fatigue is usually described as decreased responsiveness resulting from over-exertion: For example, a muscle's decreased strength or speed of contraction, or a nerve's decreased speed of conduction, or a sense organ's decreased ability to detect or to discriminate. Another meaning of fatigue, a decreased resistance or strength, can be applied to materials, as well as to some biological functions, for example when fatigue leads to sickness or infections.

"Responsiveness" implies sensitivity, and decreased sensitivity to stimulation can be seen in fatigued sense organs, nerves, muscles, and many other types of cell--immune cells, secretory cells, etc. Even plant cells have very similar processes of excitability that can be depleted by repetition.

In a series of lectures to the Royal Society in England (1895-1901), the physicist Jagadis Chandra Bose described work that at first excited, and then disturbed, many physicists and biologists. He had invented devices for both producing and detecting electromagnetic waves, and he had been the first to produce millimeter length radio waves (microwaves). In Marconi's first transatlantic radio transmission Bose's signal

GLOSSARY:

Uncoupling --In cellular respiration, oxidation of "fuel" in the mitochondrion is coupled to the phosphorylation of ADP, forming ATP. Uncouplers are chemicals that allow oxidation to proceed without producing the usual amount of ATP.

DNP--Dinitrophenol --an uncoupler that was once popular as a weight-loss drug.

NAD+ and NADH --*Nicotinamide adenine dinucleotide, and its reduced form are coenzymes for many oxidation and reduction reactions in cells.*

Hyperammonemia --The presence of too much ammonia in the blood.

Vicinal water --water near surfaces, especially hydrophobic surfaces, that is physically and chemically different from ordinary water.

Hydrophobic --insoluble in water, a non-polar oil-like molecule that repels water.

detecting device was used. This device was based on the fact that two pieces of metal in superficial contact became electrically fused (cohered) in the presence of an electrical or electromagnetic field. After they cohered, a mechanical shock would separate them, breaking the electrical fusion.

When Bose was experimenting with his "self-restoring coherer," a semiconducting device that spontaneously broke the connection without being mechanically shaken, he observed that it became insensitive after prolonged use, that is, it lost its self-restoring capacity, but that after a rest, it recovered its sensitivity. He recognized the complex behavior of his instrument as being very similar to the electrical physiology of living cells.

He then began a series of experiments on plants, animals, and minerals, that showed similar responses to all kinds of stimulation, including mechanical and thermal and electromagnetic.

The idea of metal fatigue wasn't new, but Bose was able to think far beyond the ideas of the metallurgists. Biologists were thinking of electrical responsiveness as a defining feature of life, and Bose demonstrated that plants had electrical responsiveness very similar to that of animals, but also that similar reactions could be demonstrated in minerals.

This was what disturbed the English scientists. Sensitivity, irritability, fatigue, and memory were supposed to be special properties related to life, and maybe to consciousness. For the Englishmen, there were religious implications in this Hindu's research.

There were several reasons that European and American scientists couln't accept the universal nature of the electrical properties that they were studying in animals. One of their motives was to see life as something immaterial, or of an absolutely different nature than inorganic matter. Another problem had to do with the developing belief that the special properties of life were enclosed in the hereditary substance of each cell, and that the electrical functions of cells were produced entirely by the presence of a membrane, surrounding a drop of water containing randomly moving dissolved chemicals. For the membrane electricity theory, it was essential to believe in the random behavior of things dissolved in the cell water.

So they considered the electrical-mechanical reactions and interactions of minerals to be so unlike the processes of life that it was inappropriate to see analogies between them. Minerals were composed of atoms, and, according to the doctrine of the time, they could have no integral "physiological" functions except on the atomic scale. It was more than 20 years before mainstream physicists began thinking about "delocalized" forces and fields in minerals.

Between 1915 and 1934, Michael Polanyi made many observations that made it clear that the old kind of electrical atomism was completely unfounded. The behavior of mineral crystals, and the interactions between different phases of material, such as gas or liquid with a solid, could be understood only in terms of relatively long-range forces. Polanyi's experiments showed, for example, that events on the surface of a crystal modified the strength and deformability of the crystal.

Many others between 1900 and 1940--Lepeschkin, Nasonov, Bungenberg de Jong, and Solco Tromp, for example--argued that the sensitivity of protoplasm had to be understood in terms of long range order, something like a liquid crystalline state of matter that would require some of the kinds of knowledge of matter that were being developed by physicists, metallurgists, and a variety of others investigating the condensed states of matter.

But the mainstream biologists preferred to describe cells in terms that would make impossible any of the responsivities or sensitivities seen in the "simple" solid state of minerals. To defend their ideology of the immateriality of life, they denied that the subtlest features of matter had anything to do with life, reducing life to a debased set of special, merely theoretical, mechanisms. The now defunct physical theory of merely localized atomic electrical forces became the paradigm for the new biology. The many demonstrations of coherent, ordered physical behavior of the cytoplasm, for example Gurwitch's mitogenic radiation, were dismissed with prejudice.

During G. W. Crile's long career (1889-1941), understanding shock, biological energy, and fatigue were his main concerns. He believed that shock was the result of brain exhaustion, and in one of his last publications he showed that the brains from exhausted animals produced less bioluminescence than those from rested animals. His importance was in demonstrating that fatigue and shock are systemic conditions of the organism, rather than isolated events in muscles and nerves. Recent publications are showing the validity of this view. Crile's approach to the prevention and treatment of shock was based on isolating the damaged area with local anesthetics. Blocking the nerves from one injured part of the body, for example the sciatic nerve in the leg, could preserve energy production (and normal cell functions) throughout the rest of the body.

About 30 years earlier (1901), Vvedensky had demonstrated that some types of fatigue appear to be a defensive blocking of responsiveness, such that intense stimulation would produce no response, while weak stimulation could sometimes produce a response. These changes affected cell functions in a variety of ways, that he called narcosis and parabiosis.

There have been two popular ways to "explain" fatigue, one by saying that the cell's energy (usually thought of as ATP or glycogen) is used up, the other saying that the accumulation of a metabolic product (usually lactic acid) prevents further functioning. The obvious problem with these explanations is that the fatigue response is quite independent of those metabolic changes. Another problem is that those ideas don't explain the real changes that occur in cells that are demonstrating fatigue.

Fatigued cells take up water, and become heavier. They also become more permeable, and leak. When more oxygen is made available, they are less resistant to fatigue, and when the organism is made slightly hypoxic, as at high altitude, muscles have more endurance, and are stronger, and nerves conduct more quickly. These facts don't fit with the standard model of the cell, in which its sensitivity is strictly governed by the behavior of its "membrane." (For example, how can a membrane leak large molecules at the same time that it is intact and causing the cell to swell osmotically?) They are consistent with the model of the cell that treats protoplasm as a special phase of matter.

Another feature of fatigue (and often of aging, stress, and sickness) is that the relaxation of muscles is retarded and impaired.

Hypothyroidism causes muscle relaxation to be slowed, both in skeletal muscles and in the heart. F/Z. Meerson showed that stress causes heart muscles to be exposed to increased calcium, followed by breakdown of fats and proteins, and that these changes keep the injured heart in a continuous state of partial contraction, making it stiff, and resistant to complete contractile shortening. When many cardiologists talk about the heart's stiffness, they are thinking of muscular thickening and fibrosis, but those are late consequences of the kind of contractile, unrelaxed stiffness that Meerson described.

The hypothyroid heart does eventually become fibrotic, but before that, it is just unable to relax properly, and unable to contract fully. This failure to empty fully with each contraction is a kind of "heart failure," but it can be corrected very quickly by supplementing thyroid. Even the fibrotic heart can recover under the influence of adequate thyroid.

The analogy of the "coherer" would suggest that the overstimulated muscle isn't able to decohere itself, until it has had a rest. It responds to stimulation, lets the energy flow, but then can't turn it off, and the energy keeps flowing, because of a change in physical state.

Albert Szent-Gyorgyi was probably the first person to seriously investigate the semiconducting properties of living material. Since he was aware of W.F. Koch's idea of a free radical catalyst to support oxidative metabolism, his suggestion in 1941 that cellular proteins could function as electrical conductors (or semiconductors) was very likely based on his research in cellular respiration, as well as on his work with muscle proteins. He had observed that ATP lowers the viscosity of a solution of the muscle protein myosin, and that it would cause a filament formed by precipitating myosin to contract. The polymerization and contraction of proteins under the

influence of free radicals was at the heart of F.W. Koch's therapeutic ideas, but Koch's work was about 100 years too early, by medical standards.

Szent-Gyorgyi observed that, although ATP was involved in the contraction of muscles, its post-mortem disappearance caused the contraction and hardening of muscles known as rigor mortis. When he put hardened dead muscles into a solution of ATP, they relaxed and softened. The relaxed state is a state with adequate energy reserves.

After Szent-Gyorgyi moved to the U.S., in 1947, he demonstrated the effect of muscle cytoplasm on the behavior of fluorescent substances, which was analogous to that of ice, until the muscle was stimulated. During contraction, the fluorescent material behaved as it would in ordinary liquid water. This effect involved the stabilization of the excited state of electrons. This single demonstration should have caused biologists to abandon the membrane theory of cellular excitation, and to return to basic physics for their understanding of cell behavior. The implications of Szent-Gyorgyi's work were enormous for biology and medicine, and even for the understanding of semiconductors, but most of the world was hypnotized by a simple textbook model of cell membranes.

Szent-Gyorgyi also demonstrated that the combination of properly balanced electron donors and electron acceptors (D-A pairs) would cause a muscle to contract. He compared this to "doping" an inorganic superconductor, to regulate its electronic behavior. Although these experiments were done half a century after Koch's application of free radical chemistry to medicine, they still didn't rouse the pharmaceutical industry from its toxic slumber.

I suspect that it was Szent-Gyorgyi's research with those interesting electronic properties of cellular water and proteins that in 1960 gave Linus Pauling the idea to explain anesthesia, specifically noble gas anesthesia, in terms of water clathrate formation, the restructuring of cellular water by the hydrophobic atom or molecule of an anesthetic. His suggestion caused a reaction among biologists that discouraged research into the subject for about 40 years.

Gilbert Ling's view of cytoplasmic structure gives a different emphasis to the function of electrons, which I think is an essential complement to Szent-Gyorgyi's view. Ling's emphasis is on how the inductive effect of adsorbed substances (for example, ATP and progesterone have powerful adsorptive effects) on proteins changes the charge concentration on ionizable groups. When the charge concentration is in one configuration (more acidic), the preferred counter-ion is potassium, and in another (less acidic) configuration, it is sodium.

Gilbert Ling's biophysical calculations were useful to physical chemists, and were soon put to practical use for understanding ion exchange resins, such as water softeners. Many sorts of evidence showed their validity for cell physiology, but nearly all biologists rejected them, preferring to talk about membranes, pumps, and channels, despite the evidence showing that the properties ascribed to those are simply impossible. NMR imaging (MRI) was developed by Raymond Damadian specifically as an application of Ling's description of cell physiology.

Although metals are conductors, the function of the coherers of Bose and others shows that the surface is a semiconductor, that requires the slight excitation of an electromagnetic wave to become conductive, at which point the conduction band of electrons in the metal becomes coherent and extends from one particle into the others. The surface of any phase of a substance has electronic properties distinct from those of the bulk phase, and in a sense the interface constitutes a special phase of matter. When the electrons of the interface lose their special properties, the structure of the whole system changes.

When a muscle cell is stimulated enough to cause a contraction, the interruption of its resting phase causes a shift in the charge concentration on the proteins, potassium ions are exchanged for sodium ions, calcium ions enter, and phosphate ions separate from ATP, and are replaced by the transfer of phosphate to ADP from creatine phosphate.

Since the quantum physicist E. Schroedinger wrote his book, *Time's Arrow,* people have often thought of life in terms of negentropy, going

against the general tendency of entropy to increase, except for aging and death, which are seen as obeying a law of increasing entropy. But A. Zotin investigated organisms, rather than abstractions about electrons, and shows that aging involves a ***decrease*** in entropy, and a slowing of metabolism. The decrease of entropy with aging, according to his view, would be analogous to crystallization, a sort of progressive freezing.

When a nerve is stimulated, it releases energy suddenly, and much of this heat seems to be the result of a change of structure in the cytoplasm, since (in crustaceans' nerves, which can function at low temperature) during the resting recovery of the nerve, its temperature goes slightly below the ambient temperature, despite the release of some heat from the chemical changes of metabolism, stimulated by the nerve's activity.

When a physical change is endothermic, as the nerve's recovery is, that can be interpreted as an increase in overall entropy, as when a rubber band spontaneously contracts, and becomes cooler.

Bose's rested coherer, which, with time, spontaneously recovered its semiconductive (i.e., relatively insulating) property, wasn't being powered by metabolism. As the particles returned to their relatively isolated state, there was a decrease of order, and the change was probably somewhat like the spontaneous energy change in the stimulated crustacean nerve.

Seeing the structure of the cytoplasm as something like a spring-driven mechanism, able to bounce between two states or "phases," makes it easier to see cellular fatigue as something different from the various metabolic energy sources, ATP, glycogen, and oxygen, which--contrary to conventional assumptions--aren't closely tied to the functional losses occurring in fatigue.

The role of metabolism, then, becomes analogous to the role of the "tapper" in the early forms of the coherer.

Water in its normal state is a dielectric. But when it is polarized by an electrical charge, or by the presence of a phase boundary, its normal state is altered. This is the special **interfacial** water, or **vicinal** water. With the movement of ions (mainly potassium, sodium, calcium, and magnesium) during excitation, the state of the cellular water is necessarily changed by the presence of different substances. In the excited state, cell water is less hydrophobic, more hydrophilic than in the relaxed state. A network of "hydrophobic" interactions extends through the relaxed cell. One of the properties of a dielectric is that it tends to move into the space between charges, with a force similar in principle to that involved in dielectrophoresis.

In the resting state, potassium is the main inorganic ion, and it is associated with acidic groups, such as aspartic and glutamic acid. During excitation, potassium is partly exchanged for sodium, which becomes the preferred counter-ion for the acid groups, and calcium enters the cell along with the sodium. Potassium's interaction with water is very weak (its hydration has been called negative), allowing water to form the structures that are stable in the presence of hydrophobic surfaces. Sodium and especially calcium (smaller atoms, with higher surface charge concentration) powerfully interact with water molecules, more strongly than water interacts with itself, disrupting the delicate somewhat hydrophobic structures of the intracellular water.

(Calcium, with its two charges, has important binding and stabilizing functions in the resting cell. In the excited cell, these internal calcium ions are released, while extracellular calcium ions enter the cell.)

With the increased movement of charged particles during the stimulation of a nerve or muscle, as one kind of counterion is exchanged for another, and the destruction of some of the water's structure, there are more opportunities for bulk dielectric water to enter cells, interfering with the arrangement of proteins, and tending to cause swelling and separation of the structural elements of the cell. Electron micrographs of fatigued muscle show a remarkable separation of the actin and myosin proteins.

In the excited state, NMR studies show that cell water behaves more like bulk water, that is, its molecular movements are relatively free, indicating the momentary loss of the interfacial state. In this state, the uptake of water, and the fatigue-related swelling of nerves and muscles, would be driven at least partly by the principle

that a dielectric tends to be pulled into the spaces separating charges. The bulk water that enters a cell during the breakdown of vicinal water functions as an extraneous material somewhat beyond the cell's control.

These bulk-like high dielectric properties of water in the excited cellular state can explain many changes of enzyme activity. Previously nonpolar lipids would develop a negative surface charge (from accumulating hydroxyl groups: Marinova, et al., 1996), which would tend to increase their oxidation and degradation. With the loss of the interfacial water, the cell's high energy resting state is replaced by an active mobilization of its resources, to maintain and restore the cell's structure. Metabolic energy begins to flow into the processes of restoration, serving the function of the tapper in the earliest coherers.

Looking at fatigability, muscle contraction, and nerve conduction in a variety of situations, we can test some of the traditional explanations, and see how well the newer "bioelectronic" explanation fits the facts. Osmotic pressure, hydrostatic pressure, atmospheric pressure, and the degree of metabolic stimulation by thyroid hormone affect fatigue in ways that aren't consistent with the membrane-electrical doctrine.

The production of lactic acid during intense muscle activity led some people to suggest that fatigue occurred when the muscle wasn't getting enough oxygen, but experiments show that fatigue sets in while adequate oxygen is being delivered to the muscle. Underwater divers sometimes get an excess of oxygen, and that often causes muscle fatigue and soreness. At high altitudes, where there is relatively little oxygen, strength and endurance can increase.

An excess of oxygen can slow nerve conduction, while hypoxia can accelerate it. (Increasing the delivery of oxygen at higher pressure doesn't increase the cellular use of oxygen or decrease lactic acid production in the exercising muscle [Kohzuki, et al., 2000], but it will increase lipid peroxidation.)

High hydrostatic pressure causes muscles to contract, though for many years the membrane-doctrinaires couldn't accept that. Underwater divers experience brain excitation under very high pressure. Since vicinal water has a larger volume than ordinary water (analogous to the expansion when ice is formed, though the volume increase in cell water is slightly less, about 4%, than in ice, which is 11% more voluminous than liquid water), compression under high pressure converts vicinal cell water to the state that occurs in the excited cell, the way ice melts under pressure. The excited state exists as long as water remains in that state.

These changes of state under pressure are reminiscent of Bose's use of pressure in some of his coherers, and of the fact that pressure alters the sensitivity of electrons in a semiconductor, by altering their "band gap," the amount of energy needed to make them enter the conductive zone.

One of the early demonstrations that cell water undergoes a phase change during muscle contraction involved simply measuring the volume of an isolated muscle. With stimulation and contraction, the volume of the muscle decreases slightly. (The muscle was immersed in water in a sealed chamber, and the volume decrease in the whole chamber was measured.) This corresponds to the conversion of vicinal water to bulk-like (dielectric) water. (The threatening implications of those experiments with spontaneous volume change were very annoying to many biologists of my professors' generation.)

In the stimulated state, the cell's uptake of water from its environment coincides closely with its electrical and thermal activity, and its expulsion of water coincides with its recovery. In a small nerve fiber, or near the surface of a larger fiber, these changes are very fast, and in a large muscle the uptake of water is faster than the flow of water from capillaries can match, but it will become massive if stimulation is continued for several minutes. For example, two minutes of stimulation can cause a muscle's overall weight to increase by 6%, but its extracellular compartment loses 4%, so the muscle cells gain much more than 6% of their weight in that short time (Ward, et al., 1996). The water that is taken up by cells is taken from the blood, which becomes relatively dehydrated and thicker in the process.

The belief in "semipermeable membranes" (which hasn't been a viable explanation of cell

physiology for a very long time) forces people to explain cell swelling osmotically, which means that they simply assume that the number of solute particles inside the cell has drastically increased in a very short time. In Tasaki's experiments (1980, 1981, 1982), the swelling in a nerve coincides with the electrical action potential, which, according to the osmotic explanation, means that a very large increase in internal osmolarity happened in essentially no time. The action potential comes and goes in about 2 milliseconds. The swelling also coincides with heat production and shortening of the nerve fiber. The shrinkage of the nerve fiber after the end of the action potential may be just as rapid, and the membrane theory offers no explanation for that, either. (But the restoration of the unswollen state can be very prolonged, depending on conditions extrinsic to the particular muscle or cell.) Troshin's survey of the theory of osmotic regulation of cell volume showed that the idea of the cell as a membrane osmometer was false, but very few biologists read his book.

Since the excited or fatigued muscle or nerve swells and gains weight, it's interesting to see what happens to their sensitivity and strength when they are exposed to hypotonic solutions that tend to promote swelling, or to hypertonic solutions, that help to prevent swelling.

In a hypotonic solution, cells are excited (Lang, et al., 1995: "Exposure of aortic strips from guinea-pigs to hypotonic extracellular fluid is followed by marked vasoconstriction..."), but the early excitation is followed by decreased responsiveness (Ohba, et al., 1984: "Exposure of muscle to hypotonic solutions [70% of normal solution] produced initially a transient increase in twitch after which twitch declined below the control level"). Hypertonic solutions tend to produce relaxation in normal muscles, including the aorta (Tabrizchi, 1999), but when muscle function is impaired (especially in the circulatory system, as in shock) they improve contractile function (Elgjo, et al., 1998: "The maximum contraction force measured in isolated right papillary muscles ex vivo was significantly greater in HSD-treated than normal saline-treated animals"). Athletes can lose 4% of their weight by dehydration without decreasing their muscular strength.

Hypothyroidism tends to cause loss of sodium from the blood, and the hyponatremia sometimes leads to a generalized hypotonicity of the body fluids. The thyroid hormone itself functions as an antioxidant, but much of its protective effect against cell damage is probably the result of preventing cell swelling and accelerating the removal of calcium from the cell. (Swelling, like fatigue, causes intracellular calcium to increase.)

The electrical surface charging of lipids in bulk water probably accounts for the increased lipid peroxidation that occurs in fatigue, edema, and hypothyroidism, when water loses its normal partial hydrophobicity. Increased carbon dioxide is known to decrease lipid peroxidation, and its production requires adequate thyroid function.

Thyroid stimulation of oxygen consumption tends to prevent lactic acid production, because it keeps the cytoplasm in a state of relative oxidation, i.e., it keeps the concentration of NAD+ hundreds of times higher than that of NADH. NADH is required for the conversion of pyruvate to lactate. It is also the source of reducing potential in many kinds of toxic redox cycling, that generate lipid peroxides, and it maintains the sulfhydryl system, involving the balance of reduced glutathione with the sulfhydryl-disulfide system of protein bonds, which governs the cell's electronic state and affects its balance of hydrophobicity and hydrophilicity.

The harmful lipid oxidation interferes with energy production and regulatory processes, and is responsible for some of the prolonged effects of fatigue, swelling, and hypothyroidism. These lingering effects of lipid oxidation are undoubtedly amplified by the presence of larger amounts of unstable polyunsaturated fats, as the energy demands of the fatigued state mobilize free fatty acids from the tissues.

One of the oldest tests for hypothyroidism was the Achilles tendon reflex test, in which the rate of relaxation of the calf muscle corresponded to thyroid function--the relaxation is slow in hypothyroid people. Water, sodium and calcium are more slowly expelled by the hypothyroid muscle. Exactly the same slow relaxation occurs in the hypothyroid heart muscle, contributing to congestive heart failure, because the

semi-contracted heart can't receive as much blood as the normally relaxed heart. The hypothyroid blood vessels are unable to relax properly, contributing to hypertension. Hypothyroid nerves don't easily return to their energized relaxed state, leading to insomnia, paresthesias, movement disorders, and nerves that are swollen and very susceptible to pressure damage.

With aging, hypothyroidism, stress, and fatigue, the amount of estrogen in the body typically rises. Estrogen is catabolic for muscle, and causes systemic edema, and nerve excitation. It weakens muscle contraction in the bladder, although it lowers the threshold for stimulation of sensation and contraction (Dambros, et al., 2004). This is the pattern that causes people to wake up frequently, to pass a small amount of urine. (Progesterone has the opposite effect in the urinary bladder, raising the threshold of response, but strengthening contraction, as it does in the gallbladder.) Estrogen lowers stimulation threshold in the gallbladder, as it does in the brain. Part of its excitatory action might be the result of increased hypotonic tissue water, but its effects on nerve thresholds are practically instantaneous.

In 1971 and '72, I gave some of the reasons for thinking that estrogen's biological effects result from its direct effects on cell water, causing it to become more like bulk (high dielectric) water. For example, NMR (spin echo) of estrogen treated uterus and of the uterus from an old animal were closer to bulk water than that of a young animal. Estrogen, like fatigue or excessive oxygen, slows nerve conduction.

Lactic acid production increases with fatigue, aging, hypothyroidism, estrogen excess, and other inefficient biological states. Its presence, when oxygen is available, indicates that something is interfering with efficient oxidative energy metabolism. Ammonia, free fatty acids, and various inflammatory cytokines are also likely to increase in those stress states.

A dangerously high level of ammonia in the blood (hyperammonemia) can be produced by exhaustive exercise, but also by hyperbaric oxygen (or a high concentration of oxygen), by high estrogen, and by hypothyroidism. It tends to be associated with an excess of lactic acid, probably because ammonia stimulates glycolysis. Excess oxygen, like hypothyroidism, is equivalent to "hyperventilation," in producing an abnormally low level of carbon dioxide in the blood. The Krebs cycle, during stress, is limited by the unavailability of carbon dioxide. These factors result in the waste of glucose, turning it into lactic acid, rather than carbon dioxide and energy. In these ways, the metabolism of fatigued muscle (or any cell under stress) is similar to tumor metabolism.

Hyperammonemia disturbs excitatory processes, and can cause seizures, as well as stupor, and is probably involved in mania and depression. Lithium happens to complex electronically with ammonia, and I think that accounts for some of its therapeutic effects, but carbon dioxide is the main physiological factor in the elimination of ammonia, since it combines with it to form urea. The changes in cell water in the excited/fatigued state represent an increase in the water's "structural temperature," and that would imply that less carbon dioxide could remain dissolved during excitation.

Eating sugar and using caffeine, which increases the oxidation of sugar (Yeo, et al., 2005), can reduce fatigue, both subjectively and objectively. Metabolically, they increase the production of carbon dioxide. Increasing sugar decreases the liberation and use of fatty acids, and by a variety of mechanisms, helps to lower the production of ammonia, lactate, and inflammatory cytokines. (Lactic acid, in combination with acidosis and free phospholipids, can interfere with efficient cell functions [Pacini and Kane, 1991; Boachie-Ansah, et al., 1992].) Free fatty acids release tryptophan from albumin, contributing to the formation of serotonin, which increases the sense of fatigue.

Aspirin and niacin help to prevent fatigue symptoms, and to prevent many of the harmful systemic oxidative after-effects. (Both are antilipolytic; aspirin uncouples mitochondria.)

Uncoupling of mitochondrial oxidative metabolism from ATP production helps to consume the sugar which otherwise would be diverted into lactic acid, and converts it into carbon dioxide instead. Mild hypoxia, as at high

altitude, suppresses lactic acid production ("the lactate paradox"), and increases the amount of carbon dioxide in tissues.

Aspirin and thyroid (T3) increase uncoupling. A drug that used to be used for weight reduction, DNP, also uncouples mitochondrial metabolism, and, surprisingly, it has some of the beneficial effects of thyroid and aspirin. It stimulates the consumption of lactic acid and the formation of carbon dioxide.

The squirrel monkey, which on average weighs about 2 or 3 pounds as an adult, lives much longer than other mammals of its size, usually about 20 years, as long as 27. It has an extremely high rate of oxygen consumption. This is probably the result of natural uncoupling of the mitochondria, similar to that seen in long-lived mice. Mice with 17% higher resting oxygen consumption lived 36% longer than slow respiring mice of a related strain (Speakman, et al., 2004).

Living at a high altitude, people tend to eat more and stay leaner than when they live near sea level. Apparently, their mitochondria are relatively uncoupled, and they have more mitochondria, which would partly account for their lower production of lactic acid during muscular exertion. Increased thyroid activity, too, tends to increase mitochondrial mass, as well as their uncoupling.

Most of the things that we think of as fatigue result from disturbances of the hydration of cells, whose sensitivity, composition, and structure change according to the extent of the disturbance. The hydration is governed by the cells' "electrical" properties, which are regulated by internal metabolic processes and by systemic processes. When cellular fatigue reaches a certain point, only the interactions of all the organs can restore stable cellular structure and functions. The liver eliminates lactic acid and ammonia, the adrenals and gonads provide stabilizing steroids, and the brain alters activity and behavior, in ways that can reverse most of the effects of fatigue.

But, when the tissues contain large amounts of polyunsaturated fats, every episode of fatigue and prolonged excitation leaves a residue of oxidative damage, and the adaptive mechanisms become progressively less effective. When the most powerful adaptive mechanisms, such as the timely synthesis of progesterone, pregnenolone, DHEA, T3, and the inhibitory transmitters, GABA and glycine, fail, then some of the primitive defense mechanisms will become chronically activated, and even sleep may fail to restore normal cellular water and metabolism. Hyperventilation often becomes a problem, making capillary leakiness worse.

Water in the body occupies three major compartments--blood vessels, extracellular matrix, and the moist cell substance itself--and its condition in each compartment is a little different, and subject to variation. There are no textbooks in use in the U.S. that treat intracellular water scientifically, and the result is that physicians are confused when they see patients with edema or with disturbances in blood volume. It rarely occurs to physicians to consider disturbances of water distribution in problems such as chronic fatigue, fibromyalgia, sleep disturbances, frequent urination, slow bladder emptying, anxiety, paresthesia, movement disorders, the tunnel syndromes, or even slowed thinking, but "intracellular fatigue" leading to over-hydration is probably the central problem in these, and many other degenerative and inflammatory problems.

The improvements in cell functions and water distribution that are inversely related to oxygen pressure, and directly related to carbon dioxide, won't be discussed in medical textbooks until they have given up the idea of membrane-regulated cells.

The "treatment" for intracellular fatigue consists of normalizing thyroid and steroid metabolism, and eating a diet including fruit juice, milk, some eggs or liver, and gelatin, assuring adequate calcium, potassium, sodium, and magnesium, and using supplements of niacinamide, aspirin, and carbon dioxide when necessary. Simply increasing carbon dioxide decreases lactic acid and ammonia, increases GABA (the sleep improving nerve inhibitor), and regulates mineral and water disposition.

One of the outcomes of the study of the physiology of fatigue is that it leads to a better understanding of cells in general, and offers some new insights into aging, inflammation, and a variety of stress-related diseases.

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Ray Peat's Newsletter

The cistern contains: the fountain overflows. **W. Blake**

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Regeneration and degeneration:

Types of inflammation change with aging

For about 100 years it has been popular to explain the degenerative diseases as the result of mutations in the genes, a slow accumulation of "somatic mutations," as opposed to the "germ cell mutations" that are involved in Huntington's chorea and sickle cell anemia. Some people explained all the changes of aging on the same basis, but 50 years ago, the somatic mutation theory of aging was clearly shown to be false. The gene-mutation theory of cancer is more persistent, but the work of people like Harry Rubin has made it clear that functional changes in cells that are becoming cancerous destabilize the chromosomes and cause defects to appear in the genes, rather than the reverse.

Older ways of understanding aging and degenerative disease are now returning to the foreground. The developmental interactions of the organism with its environment, and the interactions of its cells, tissues, and organs with each other, have again become the focus of biological aging research. In place of the old belief that "we are defined and limited by our genes," the new perspective is showing us that we are limited by our environment, and that our environment can be modified. As we react to unsuitable environments, our internal environments become limiting for our cells, and instead of renewing themselves, repairing damage, and preparing for new challenges, our cells find themselves in blind alleys. Looking at aging in this way suggests that putting ourselves into the right environments could prevent aging.

A bird developing inside its egg shell illustrates the way organs and the environment interact. The chicken created a very good environment for the early development of its young. When the egg is formed, it contains everything needed to produce a chicken, except for oxygen and a steady warm temperature. But before the chick's body has finished developing, using yolk fat for energy, the glucose contained in the egg has been consumed, and at that point the chick's brain stops growing. A researcher who knew that brain growth in other kinds of animal requires glucose, injected glucose (or glycine) into the developing eggs when the original glucose had been depleted. The supplemental glucose allowed the chick's brain to continue growing until it hatched. These chicks had larger brains, containing more numerous cells. The same experimenters also found that progesterone increases brain size, while corticosterone decreases it. Although the egg is a very good environment for the development of chickens, these experiments showed that it isn't the best that can be achieved. If the hen's environment had been different, it might have been able to provide as much glucose and progesterone as the experimenters did.

Mammals were able to develop bigger brains than birds, by gestating their offspring internally, allowing a continuous supply of nutrients, such as glucose, and hormones such as progesterone. But the environment of the mother still can profoundly affect the development of the offspring, by influencing her physiology.

Another factor involved in developing a large brain is the metabolic rate, which is closely associated with the temperature. Birds have larger brains relative to their bodies than reptiles do, and birds maintain a consistently high body temperature, sometimes as high as 110 degrees F, while reptiles' temperature varies somewhat according to the temperature of their surroundings and their level of activity. Amphibians have much lower metabolic rates, and are generally unable to live at

the higher temperatures required by reptiles.

The high metabolic rate of a bird, combined with its development inside an egg, means that compromises are made. The high rate of metabolism uses the stored energy rapidly, so the growth of the brain is limited. But their very high body temperature maximizes the effectiveness of that brain. Birds, such as owls, parrots, and crows, that hatch in a less developed, more dependent condition, are able to continue their brain growth, and have larger brains than other birds, such as chickens. In birds and mammals, longevity generally corresponds to brain size and metabolic rate. (For example, a pet crow, Tata, died at the age of 59 in 2006 in New York; parrots sometimes live more than 100 years.) These (altricious) birds are the opposite of precocious, they preserve embryonic or infantile traits into adulthood.

For whole organisms or for single cells, development depends on the adequacy of the environment. Temperature and the quality of nourishment are important, and by thinking about the other special features of the growth processes during gestation, we might be able to find that some of the compromises that are customarily made in our more mature lives aren't necessary.

One way of looking at aging is that it's a failure of regeneration or healing, related to changes in the nature of inflammation.

In childhood, wounds heal quickly, and inflammation is quickly resolved; in extreme old age, or during extreme stress or starvation, wound healing is much slower, and the nature of the inflammation and wound closure is different. In the fetus, healing can be regenerative and scarless, for example allowing a cleft palate to be surgically corrected without scars (Weinzweig, et al., 2002).

Fifty years ago, inflammation was seen as a necessary part of the healing process, but now it is recognized as a cause of heart disease, diabetes, cancer, and aging itself. During the development of the organism, the nature of healing changes, as the nature of inflammation changes. Early in life, healing is regenerative or restorative, and there is little inflammation. In adulthood as the amount of inflammation increases, healing fails to completely restore lost structures and functions, resulting in scarring, the replacement of functional tissue with fibrous tissue. Identifiable changes in the nature of inflammation under different conditions can explain some of these losses of healing capacity. Factors that limit inflammation and fibrosis, while permitting tissue remodeling, could facilitate regeneration and retard aging.

Several cytokines (proteins that regulate cell functions) appear at much higher concentrations in adult tissues than in fetal tissues (PDGF A, three forms of TGF, IGF 1, and bFGF; Wagner, et al., 2007), and when one of these (TGF-beta1) is added to the healing fetus, it produces inflammation and fibrosis (Lanning, et al., 1999). Two prostaglandins, PGE2 and PGF2a, potently produce inflammation in fetal rabbits, but not in adult rabbits. (Morykwas, et al., 1994).

Tissue injury that would produce inflammation in adults causes other signals in the fetus that activate repair processes. When a cell is injured or stressed, for example when deprived of oxygen, it becomes incontinent, and releases ATP into its surroundings. The extracellular ATP, and its breakdown products, ADP, AMP, adenosine, and inorganic phosphate or pyrophosphate, stimulate cells in various ways. ATP causes vasodilation, increasing circulation, and usually signals cells to divide, and can activate stem cells (Yu, et al., 2010) The lactic acid produced by distressed cells also has signalling effects, including vasodilation and stimulated division. Stressed cells digest their own proteins and other structural materials (autophagy), and the breakdown products act as signals to guide the differentiation of their replacement cells. Mobile phagocytes, ingesting the material of decomposing cells, are essential for guiding tissue restoration.

In adults, prostaglandins are known to be involved in many of the harmful effects of inflammation. They are formed from the polyunsaturated fats, linoleic acid and arachidonic acid, which we are unable to synthesize ourselves, so the adult's exposure to the prostaglandins is influence by diet. Since the fetus is able to synthesize fat from glucose, the newborn animal usually contains a high proportion of saturated fats and their derivatives, such as stearic acid, oleic acid, and Mead acid, which can be synthesized from glucose or amino acids. Newborn calves have very little

polyunsaturated fat in their tissues, but even the small percentage of PUFA in milk causes its tissues to gradually accumulate a higher percentage of PUFA as it matures. The fatty acids of newborn humans, and other non-ruminants, reflect their mothers' diets more closely, but Mead acid is still present in human newborns (Al, et al., 1990). In a study of prenatal learning (habituation rate), the experimenters found that the relative absence of the supposedly essential fatty acids improved the short term and long term memory of the fetus (Dirix, et al., 2009). The size of the baby was found to be negatively associated with the highly unsaturated fatty acids DHA and AA (Dirix, et al., 2009), showing a general growth-retarding effect of these environmentally derived fats.

The embryo or fetus is enclosed in a germ-free environment, so it doesn't need an "immune system" in the ordinary sense, but it does contain phagocytes, which are an essential part of development, in the embryo, as well as in the adult (Bukovky, et al., 2000). They are involved in removing malignant cells, healing wounds, and remodeling tissues. In adults, the long-chain omega-3 fatty acids such as DHA are known to be immunosuppressive, but in tests on monocytes from the umbilical cord blood of newborns, the highly unsaturated fatty acids kill the monocytes that are so important for proper development and regeneration (Sweeney, et al., 2001), and interfere with signals that govern their migration (Ferrante, et al., 1994). DHA is now being sold with many health claims, including the idea that adding it to baby formula will improve their eyesight and intelligence. As the consumption of PUFA has increased in the US and many other countries, the incidence of birth defects has increased. The formation of excessive amounts of prostaglandin, or killing macrophages, among other toxic effects, might be responsible for those visible anatomical changes during growth, as well as for the subtler loss of regenerative capacity.

In the adult, the PUFA and prostaglandins are known to increase collagen synthesis. Serotonin and estrogen, which interact closely with PUFA, promote collagen synthesis and fibrosis. In the fetus, hyaluronic acid, rather than collagen, is the main extracellular material in wound repair (Krummel, et al., 1987). Both it and its decomposition products have important regulatory "signal" functions in wound healing (Gao, et al., 2008), inflammation, and cell differentiation (Krasinski and Tchórzewski, 2007).

Prostaglandins also inhibit local cell division (observed in the cornea, Staatz and Van Horn, 1980), shifting responsibility for tissue repair to mobile cells, for example stem cells from the blood. PUFA also interfere with the turnover of collagen by inhibiting proteolytic enzymes that are necessary for tissue remodeling. These are among the changes that characterize scar formation, rather than the scarless regeneration that can occur in the fetus. They also occur throughout the body with aging, as part of a progressive fibrosis.

Besides minimizing dietary PUFA, other things are known that will reduce the fibrosis associated with injury, inflammation, or aging. Thyroid hormone, progesterone, and carbon dioxide all reduce inflammation while facilitating normal tissue remodeling. Fibrosis of the heart and liver, which are often considered to be unavoidably progressive, can be regressed by thyroid hormone, and various fibroses, including breast, liver, and mesentery, have been regressed by progesterone treatment.

The thyroid hormone is necessary for liver regeneration, and the ability of the thyroid gland itself to regenerate might be related to the also great ability of the adrenal cortex to regenerate--the cells of these endocrine glands are frequently stimulated, even by intrinsic factors such as T3 in the thyroid, and seem to have an intrinsic stem-cell-like quality, turning-over frequently. Secretion of stimulating substances is probably one of the functions of macrophages in these glands (Ozbek & Ozbek, 2006) The failure to recognize the glands' regenerative ability leads to many inappropriate medical treatments.

The amount of disorganized fibrous material formed in injured tissue is variable, and it depends on the state of the individual, and on the particular situation of the tissue. For example, the membranes lining the mouth, and the bones and bone marrow, and the thymus gland are able to regenerate without scarring. What they have in common with each other is a relatively high ratio

of carbon dioxide to oxygen. Salamanders, which are able to regenerate legs, jaw, spinal cord, retina and parts of the brain (Winklemann & Winklemann, 1970), spend most of their time under cover in burrows, which besides preventing drying of their moist skin, keeps the ratio of carbon dioxide to oxygen fairly high.

The regeneration of finger tips, including a well-formed nail if some of the base remained, will occur if the wounded end of the finger is kept enclosed, for example by putting a metal or plastic tube over the finger. The humidity keeps the wound from forming a dry scab, and the cells near the surface will consume oxygen and produce carbon dioxide, keeping the ratio of carbon dioxide to oxygen much higher than in normal uninjured tissue.

Carbon dioxide is being used increasingly to prevent inflammation and edema. For example, it can be used to prevent adhesions during abdominal surgery, and to protect the lungs during mechanical ventilation. It inhibits the formation of inflammatory cytokines and prostaglandins (Peltekova, et al., 2010, Peng, et al., 2009, Persson & van den Linden, 2009), and reduces the leakiness of the intestine (Morisaki, et al., 2009). Some experiments show that as it decreases the production of some inflammatory materials by macrophages (TNF: Lang, et al., 2005), including lactate, it causes macrophages to activate phagocytic neutrophils, and to increase their number and activity (Billert, et al., 2003, Baev & Kuprava, 1997).

Factors that are associated with a decreased level of carbon dioxide, such as excess estrogen and lactate, promote fibrosis. Adaptation to living at high altitude, which is protective against degenerative disease, involves reduced lactate formation, and increased carbon dioxide. It has been suggested that keloid formation (over-growth of scar tissue) is less frequent at high altitudes (Ranganathan, 1961), though this hasn't been carefully studied. Putting an injured arm or leg into a bag of pure carbon dioxide reduces pain and accelerates healing.

In aging, the removal of inactive cells becomes incomplete (Aprahamian, et al., 2008). It is this removal of cellular debris that is essential for regenerative healing to take place. Degenerating tissue stimulates the formation of new tissue, but this requires adequate cellular energy for phagocytosis, which requires proper thyroid function. "Hyperthyroidism" has been shown to accelerate the process (Lewin-Kowalik, et al., 2002). The active thyroid hormone, T3, stimulates the removal of inactive cells (Kurata, et al., 1980).

Regenerative healing also requires freedom from substances that inhibit the digestion of the debris. The great decline in proteolytic autophagy that occurs with aging (Del Roso, et al., 2003) can be reduced by inhibiting the release of fatty acids. This effect is additive to the antiaging effects of calorie restriction, suggesting that it is largely the decrease of dietary fats that makes calorie restriction effective (Donati, et al., 2004, 2008).

Niacinamide is a nutrient that inhibits the release of fatty acids, and it also activates phagocytic activity and lowers phosphate. It protects against the development of scars in spinal cord injuries, facilitates recovery from traumatic brain injury, and accelerates healing generally. While it generally supports immunity, it's protective against autoimmunity. It can cause tumor cells to either mature or disintegrate, but it prolongs the replicative life of cultured cells, and protects against excitotoxicity.

The amounts needed seem large if niacinamide is thought of as "vitamin B3," but it should be considered as a factor that compensates for our unphysiological exposure to inappropriate fats. Aspirin and vitamin E are other natural substances that are therapeutic in "unnaturally" large amounts because of our continual exposure to the highly unsaturated plant-derived n-3 and n-6 fats.

When animals are made "deficient" in the polyunsaturated fatty acids, their wounds heal, with normal or accelerated collagen synthesis, and with more vigorous collagen breakdown (Parnham, et al., 1977). Their blood vessels are more resistant, preventing shock that would otherwise be caused by many factors. All phases of development, from gestation to aging, are altered by the presence of the unsaturated fats, and these effects correspond closely to the loss of the regenerative capacity, the ability to replenish and restore tissues.

If the very small amounts of polyunsaturated fats

reaching the fetus can retard growth and brain development (Liu and Borgman, 1977; Borgman, et al., 1975) and function, it is apparently acting on some very important biological processes. The toxic effects of PUFA seen in the animal studies probably have their equivalent in humans, for example the association of childhood hyperactivity with a smaller brain. The incidence of the attention deficit-hyperactivity disorder is increasing in the US, somewhat faster among girls than boys (Robison, et al.,2002). In schizophrenic teenagers, the brain shrinks, suggesting an interaction of the hormones of puberty with environmental toxins or deficiencies. The progressive accumulation of much larger amounts of these fats later in life, especially after the rate of growth decreases, could be expected to cause even greater interference with those processes of development and function.

All tissues age, but the brain might be the least ambiguous organ to consider. The aging brain often shrinks, and becomes more susceptible to excitotoxicity, which kills brain cells. Degenerative brain diseases, such as Huntington's chorea and Creutzfeld-Jacob disease, have been compared to the dementia of pellagra, in which chorea and other excitatory processes are obvious. (Anti-glutamatergic drugs are beginning to be used therapeutically, to restore some inhibitory balance in the degenerating brain.)

Pellagra occurs about twice as often in women as in men, and this is because estrogen activates an enzyme that alters metabolism of tryptophan, blocking the formation of niacin. The alternative products include the excitotoxin, quinolinic acid, and some carcinogens. Progesterone inhibits the activity of that enzyme. **Progesterone also lowers brain serotonin (Izquierdo, et al., 1978), decreases the excitatory carcinogens (Moursi, et al., 1970) and increases the formation of niacin (Shibata, et al., 2003) The polyunsaturated fats, DHA, EPA, and linoleic acid activate the conversion of tryptophan to quinolinic acid (Egashira, et al., 2003, 2004), and inhibit the formation of niacin (Egashira, et al., 1995).**

The normal pathway from tryptophan to niacin leads to formation of the coenzyme NAD, which is involved in a great variety of cellular processes, notably energy production, the maintenance of the cellular differentiated state by regulating gene expression, and the activity of phagocytes.

Glucose and niacinamide work very closely with each other, and with the thyroid hormone, in the maintenance and repair of cells and tissues. When one of these energy-producing factors is lacking, the changes in cell functions -- a sort of pre-inflammatory state -- activate corrective processes. Energy depletion itself is an excitatory state, that calls for increased fuel and oxygen. But when cells are exposed to PUFA, their ability to use glucose is blocked, increasing their exposure to the fats. Saturated fats activate the pyruvate dehydrogenase enzyme that is essential for the efficient use of glucose, while PUFA block it. (The MRL mouse strain has a high regenerative ability, associated with a retained tendency to metabolize glucose rather than fatty acids.) The negative energetic effects of PUFA include interfering with thyroid and progesterone. The energy resources are suppressed, at the same time that the inflammatory signals are amplified, and many regulatory pathways (including the replenishment of NAD from tryptophan) are diverted.

In the fetus, especially before the fats from the mother's diet begin to accumulate, signals from injured tissue produce the changes that lead quickly to repair of the damage, but during subsequent life, similar signals produce incomplete repairs, and as they are ineffective they tend to be intensified and repeated, and eventually the faulty repair processes become the main problem. Although this is an ecological problem, it is possible to decrease the damage by avoiding the polyunsaturated fats and the many toxins that synergize with them, while increasing glucose, niacinamide, carbon dioxide, and other factors that support high energy metabolism, including adequate exposure to long wavelength light and avoidance of harmful radiation. As long as the toxic factors are present, increased amounts of protective factors such as progesterone, thyroid, sugar, niacinamide, and carbon dioxide can be used therapeutically and preventively.

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(20C10S), 20% casein + 10% linoleic acid diet (20C10L), 40% casein + 10% stearic acid diet (40C10S), or **40% casein + 10% linoleic acid diet (40C10L)** for 8 days, and serum quinolinic acid concentration and ACMSD activity were determined. Serum quinolinic acid **concentration was significantly increased in the 40C10L** group compared with other three groups. There was also the negative correlation between the sum of liver and kidney ACMSD activities, and serum quinolinic acid concentration per tryptophan intake ($r = 0.8209$, $p < 0.01$). **Increased serum QA concentrations are probably due to a decreased ACMSD activity.**

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Ray Peat's Newsletter

"Reason can answer questions, but imagination has to ask them." Ralph W. Gerard

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Autoimmunity

The thymus gland is important for growth and fertility, but it is now considered to be an important regulator of the immune system. As the gland shrinks with aging, the incidence of "autoimmune diseases" increases, possibly because the regulatory functions of the gland have been lost.

It has been shown that radiation, polyunsaturated fatty acids, estrogens, and heavy metals and other toxins including dioxins damage the thymus gland, and can produce immunodeficiency. These stressors also stimulate the "autoimmune" antibodies.

Estrogen shrinks the thymus and blocks NK cells, and blocks cell division in thymic cells. Thyroid stimulates regeneration of the thymus, even after age-related atrophy. Progesterone protects against the thymic atrophy produced by stress and cortisol, and promotes thyroid's effects, and protects against many of the conditions that are called "autoimmune." Estrogen creates both immunodeficiency and autoimmune degenerative conditions.

Hypothyroidism causes the thymus gland to atrophy (Abou-Rabia and Kendall, 1994), partly because the thyroid hormone itself is essential for the maintenance of the gland, and also because hypothyroidism is likely to be accompanied by excessive levels of estrogen and cortisol.

Polyunsaturated fatty acids interfere with the formation of the thyroid hormones, by preventing the coupling reaction, which converts iodotyrosine residues into iodothyronine residues in the thyroglobulin. The resulting abnormal thyroglobulin is antigenic.

Animals that are fed diets that completely lack the polyunsaturated fatty acids appear to be free of the autoimmune diseases: their tissues can even be transplanted into other animals with less antigenicity than is normal, so the dietary polyunsaturated fatty acids seem to be involved in the development of the abnormally increased antigenicity of the various autoimmune degenerative diseases.

Several years ago, I wrote about Metchnikov's theory of immunity, based on the role of the phagocyte in the organism's ordinary growth, and I also argued that inflammation was a pathological reaction, rather than being a healthy part of a defensive immune system. Since then, the role of inflammation has been recognized in heart and circulatory disease, Alzheimer's disease, and other diseases, and even in obesity, diabetes, depression, and osteoporosis, so that now it isn't a universal medical reflex to think of inflammation as a purely normal physiological response. However, the history of treating inflammation as part of "the immune system" has left a residue of medical ideology, in which a pathogenic organism must be invoked as the cause of any inflammation, even though the concept of "sterile inflammation" has a strong foundation of evidence.

Metchnikov's view, that the "immune system" is a constructive part of normal physiology, combined with the idea of inflammation as a pathological hindrance to normal functioning and development, forms the framework for a major reconsideration of the functions of antibodies, the thymus gland, lymphocytes, and other parts of "the immune system." A few people (Jamie Cunliffe and Polly Matzinger, for example) are working on this new paradigm of "immunity," challenging the "assumption that the immune system . . . has evolved to find, kill and eliminate foreign organisms." If they are right, then all of medical thinking about immunity since Metchnikov's ideas were discarded has been, effectively, an attack against a full and proper understanding of the nature of the organism, and specifically has led to a deep misunderstanding of growth, regeneration, aging, cancer, and the

functions of nerves, hormones, and tissue interactions.

A pathogen is usually defined as an organism or a substance that causes tissue damage. I think the definition should be "a substance or process that causes tissue damage," to include the pathogenic effects of malnutrition, stress, and radiation, for example. The consequences of tissue damage have to be distinguished from the causes of tissue damage. The failure to distinguish cause and effect has led to many foolish medical theories.

The new orientation toward the immune system is that its main function is to clean up the debris created by developmental processes (such as the elimination of red blood cells, or the regression of the tadpole's tail), or by injury, and to prepare the system for recovery or regeneration. This orientation brings together ideas from developmental biology and immunology in a very encouraging way. For example, a recent study shows that "autoimmune" antibodies are involved in brain repair after traumatic injury. (Hofstetter, et al., 2003.)

The example of the tadpole's tail provides a metaphor that might be useful in understanding the ways in which hormones and the immune system interact in mammals and people. Without the thyroid hormone, a tadpole keeps its tail, and fails to turn into a frog, though it keeps growing. The thyroid hormone causes the animal to progress to a higher stage of development, in which it has a higher metabolic rate and uses lungs rather than gills. The phagocytic cells rapidly consume the structures that were appropriate for the lower stage of development and metabolism.

I think we can see analogous processes in the functioning of our immune system. When cells in any part of the body aren't able to maintain an efficient energy metabolism, they tend to be replaced by new, more active cells, and the debris of the old cells is removed by phagocytosis, often without detectable inflammation. Stimulation and adaptation are always causing remodeling of our bodies, with bones growing along lines of stress, areas of the brain expanding with learning, and organs such as the intestine and liver modifying their metabolism according to diet and exposure to toxins.

Inflammation, atrophy, or tumefaction can occur when some part of the regenerative and developmental process is defective. A failure of energy metabolism can be seen in each of these types of problem. Usually, prolonged inflammation leads to atrophy and fibrosis, which in turn increases the likelihood that a tumor will develop.

Two organs that can change their mass greatly in a short period of time are the thyroid and the thymus.

The thyroid can be functionally suppressed, and, with stimulation, return to full activity within a few hours. If it is stimulated continuously, it can increase its mass greatly in a few days. The thymus can lose most of its mass in a few hours.

The remarkable ability of the thymus gland to shrink rapidly when it's exposed to estrogen or stress or cortisol is very probably related to the fact that "cleaning up messes" is a primary function of many of the cells that constitute it.

Most of the cells of the thymus are very dependent on sugar metabolism, and this is disturbed by stress, cortisol, estrogen, and some kinds of fat. Even under normal conditions, there is a rapid turnover of its cells. Many of the cells that make up the thymus, like leukocytes generally, are highly sensitive to anything that limits their energy.

These changes in the size and composition of the thyroid and thymus glands involve some of the biochemical processes that are involved in the developmental changes in tadpoles and frogs.

Inflammation occurs when the production of debris is too rapid for its quiet removal, as when energetic process fail, or when certain specialized organisms interact destructively with the tissues. The characteristic changes in metabolism, a shift toward the production of lactic acid and the breakdown of protein, are probably as much the cause of inflammation, as its effect.

Estrogen is an important regulator of energy metabolism, and it is therefore crucially involved in the diseases known as "autoimmune diseases."

Progesterone, thyroid, and various nutrients including vitamin E, oppose the actions of

estrogen, and so have a role in the prevention of the "autoimmune diseases."

These diseases include rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, Devic's optic neuritis, cystitis, and various types of hepatitis and nephritis and pancreatitis.

Aging and stress are estrogenic, and this estrogen effect leads to atrophy of the thymus, combined with inflammation. The associated cortisol excess decreases the inflammation, but aggravates the disregulation of the immune system. Serotonin is another stress-related factor that produces involution of the thymus (Bliznakov, 1980).

The thymus gland permits immune cells to mature and to become organized. It is a major factor in the regulation of the cells that produce antibodies, the B (bone marrow derived) lymphocytes, and when the thymus is chronically damaged, the production of antibodies tends to increase, but without the sensitive control the thymus provides. Thymus-type cells are produced not just in the thymus, but also in other organs, especially the liver.

In the young organism, the disruption of a tissue exposes a variety of antigens from the differentiated cells. Antibodies that are formed to these antigens have two very different functions. They stimulate the removal of the defective cells and debris, and they locally obscure the specifically differentiated tissue components, creating a sort of vacuum to be filled by the multiplication of undifferentiated "stem" cells, which repair the damaged region.

One line of research in developmental biology emphasizes the innate tendency of cells to grow and multiply, with differentiation and growth inhibition being the subsequent result of interactions with their environment.

For many years, researchers such as Szent-Gyorgyi searched for general or specific inhibitors of cellular multiplication. Szent-Gyorgyi gave the name "retin" to a molecule that he thought could restrain cancer growth. Leonell Strong studied liver extracts, and found several anticancer agents. W.S. Bullough extracted materials that were tissue specific, that he thought might synergize with adrenaline in restraining tissue growth.

About 50 years ago, an experiment with developing frogs' eggs encouraged this line of research. The experimenter found that when the juice extracted from a particular tissue was added to the water in an aquarium where frog eggs were starting to develop, the developing embryo had a deficiency of that particular tissue, and its development would stop when the absence or deficiency of that tissue became limiting. In rats, a similar organ-specific substance had been suggested by removing part of the liver of one rat of a pair that shared the same blood supply. The livers of both animals grew until the total mass was appropriate for two animals, but the operated liver stopped growing prematurely, apparently because a circulating growth inhibiting substance reached a certain level. Bullough's term "chalone" has been generally accepted as the name for such growth inhibiting substances.

I suspect that the immune system, and the "autoantibodies," can have a function complementary to that of the chalones, possibly by blocking the release of chalones.

In 1970, I. Hellstrom and K.E. Hellstrom showed that cancer growth is promoted by an antibody, and later they showed that antagonists to that antibody would allow the cancer to be suppressed. Their work is still progressing, and it is probably relevant to both the chalone theory, and to the processes of autoimmunity and tissue regeneration. Proper control in the immune system is very closely associated with the processes that maintain a proper balance between tissue growth and tissue atrophy. Too much of an anti-chalone agent would produce a tumor, but too little would lead to atrophy when stress-damaged tissues weren't replaced.

Recent work by M. Bissell and V. Weaver shows results parallel to the Hellstroms', but involving the interactions of cells, extracellular matrix, and antibodies.

The healthy thymus gland, which depends on a properly functioning thyroid gland, is essential for close regulation of the antibody-producing cells. With aging and the various stressors, the immune system tends to over-produce antibodies, as the cell-mediated process become weaker. This is similar to the changes produced by estrogen (for

example, see Ansar Ahmed, et al., 1989). It's generally accepted that the thymus is responsible for preventing the production of autoimmune antibodies. I suspect that its actions are more subtle, and that it is (or can be) involved in developmental and regenerative processes.

Animal studies of autoimmune degenerative diseases show that estrogen promotes autoimmunity, and that progesterone alleviates or prevents some of the typical autoimmune diseases. Their antagonistic effects on the mediators of inflammation are probably responsible, as well as their opposite effects on the activation of retroviruses and stress (or "heat shock") proteins.

Systemic lupus erythematosis, rheumatoid arthritis, and other autoimmune diseases are usually corrected by the combined use of progesterone and thyroid, both of which help to restore the thymus gland.

Although medical people have been taught to believe that aging isn't an estrogenic state, contrary to the clear evidence that estrogen production (by the aromatase enzyme) in many tissues increases with age, an experiment (Greenstein, et al., 1992) has demonstrated that giving an aromatase inhibitor to old rats causes their thymus to regenerate. Now that commercial aromatase-inhibiting drugs are coming onto the market, this experiment should be of considerable interest to people involved in cancer treatment, but its implications are so important that most researchers and therapists will prefer to forget it.

The estrogenic state of old age or of stress (with increased exposure to cortisol) is partly the result of the progressive decrease in thyroid and progesterone, which is closely associated with the decline in respiratory function and mitochondrial efficiency.

The declining energy functions increase the demand for an efficient immune system, especially when we see the immune system as a regulator of tissue repair and restoration.

The accumulation of polyunsaturated fats contributes to all phases of this process of holistic decline, from the decrease of the crucial respiratory enzyme cytochrome c oxidase, through decreased thyroid hormone activity and progesterone activity, to the activation of aromatase and estrogen and the production of tissue antigens by toxic products of lipid peroxidation.

A study in Hawaii found that men who ate tofu were more likely to have dementia and brain atrophy than men who ate a standard "western" diet. Soybeans contain estrogenic chemicals, such as genistein. In Alzheimer's disease brain metabolism is low. Genistein, like other estrogens, causes the thymus gland to atrophy (Yellayi, et al., 2002). Since Alzheimer's disease is now often considered to be an "autoimmune" disease (Grainger and Reckless, 2003; Kellet, et al., 1982; Lal and Forster, 1988; Bradford, et al., 1989), both preventive and curative approaches should probably concentrate on protecting and restoring the energy metabolism and the thymus gland.

Besides the systemic toxic effects of dietary polyunsaturated fats, those fats appear to be a major factor in making tissues susceptible to damage from immunological reactions, since the tissues of rats that are deficient in the "essential fatty acids" are not damaged by antibodies that would seriously injure or kill "normal" tissues. (Takahashi, et al., 1992; Schreiner, et al., 1988). These animals are also resistant to many toxins, including endotoxin.

The unsaturation of tissue lipids increases in aging animals, along with the increased production of estrogen and decreased production of pregnenolone, progesterone, and the T3 component of the thyroid hormone. Autoimmunity increases with aging, as the thymus gland atrophies. A program to prevent or correct autoimmunity should also help to reverse the very generalized inflammatory and atrophic processes of aging. Restoration of tissue lipids (especially cardiolipin, which activates the crucial respiratory enzyme) to the high-energy state of childhood would be a central part of such a program. (See for example Paradies & Ruggiero, 1991; Paradies, et al., 1997.)

Antibodies to cardiolipin are promoted by excess estrogen (Ahmed & Verthelyi, 1993), and this is probably related to estrogen's antirespiratory actions.

Rather than viewing autoimmune diseases as irreversible degenerative conditions, I think they should be viewed as problems of metabolic

energy, processes of self-repair that just need a little support from improved diet and other environmental conditions. (See Hofstetter, et al., 2003).

REFEREBCES

Cell Tissue Res 1994 Sep;277(3):447-55. **Involution of the rat thymus in experimentally induced hypothyroidism.** Abou-Rabia N, Kendall MD. The thymus, as part of the immune-neuroendocrine axis, is greatly influenced by factors from most endocrine glands, especially the thyroid. Antithyroid drugs (carbimazole and methimazole) were used to induce hypothyroidism in rats. Histological and ultrastructural examination of the thymus showed progressive thymic involution after 4 weeks of drug treatment to the end of observations (7 weeks). The involution was characterised by increased thymocyte apoptosis and thymocyte phagocytosis by macrophages. This resulted in thymocyte depopulation, increases in numbers of interdigitating cells, alterations to mainly subcapsular and medullary epithelial cells, an apparent increase of mast cells and collagen in the capsule and septa, and increased numbers of B cells and plasma cells. Lymphoid cells immuno-reactive with MRC OX12 (which detects B cells) were observed within blood vessel walls, suggesting that they may have been moving in and out of the thymus. The administration of drugs causing hypothyroidism, therefore, also caused marked involution of the thymus.

J Autoimmun 1993 Jun;6(3):265-79 **Antibodies to cardiolipin in normal C57BL/6J mice: induction by estrogen but not dihydrotestosterone.** Ahmed SA, Verthelyi D "Autoantibodies against cardiolipin, a phospholipid, have been demonstrated in a variety of pathological states including several autoimmune conditions in humans and in certain lupus-prone mice." "Similarly, estrogen treatment of female mice further augments the incidence and the levels of these autoantibodies. Estrogen-treated mice also have antibodies reactive against other membrane phospholipids including phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylcholine (PC) and phosphatidylethanolamine (PE)." "To our knowledge, this is the first report on the demonstration of antiphospholipid autoantibodies in normal mice and induction of these antibodies by estrogen."

J Autoimmun 1989 Aug;2(4):543-52. **Estrogen induces the development of autoantibodies and promotes salivary gland lymphoid infiltrates in normal mice.** Ahmed SA, Aufdemorte TB, Chen JR, Montoya AI, Olive D, Talal N "Sex hormones influence the immune system throughout life including postnatal and prenatal stages. For example, we find that administration of estrogen to normal mice markedly augments the ability of CD5+ B cells to express their autoimmune potential by producing increased numbers of plaque-forming cells (APFC) to bromelain-treated mouse erythrocytes (Br-ME)." "We hypothesize that an imbalance of the in utero sex hormone microenvironment critically influences the fetal immune system. **We have termed this influence immunological imprinting.** After birth this imprinting could contribute to immune-mediated disorders. To test this hypothesis, we developed a mouse model in which normal mice were prenatally exposed to estrogens. In preliminary experiments, these mice produced higher numbers of APFC to Br-ME, particularly in the peritoneal cavity cell exudates. Furthermore, mice prenatally exposed to estrogens had accelerated development of autoimmune salivary gland lesions indistinguishable from Sjogren's syndrome (SS) in humans. Further experiments are warranted to confirm these findings. The prenatal effects of estrogen may have relevance for familial and neonatal autoimmune syndromes."

J Immunol 1989 Apr 15;142(8):2647-53. **Estrogen induces normal murine CD5+ B cells to produce autoantibodies.** Ansar Ahmed S, Dauphinee MJ, Montoya AI, Talal N "Females have better humoral immune responses and are more susceptible to autoimmune diseases than males." "The increased autoantibody production in females can be attributed to the effect of estrogen on the immune response because this hormone markedly augments APFC to Br-ME in intact or orchidectomized males. Male hormone had little effect. Importantly, estrogen did not increase the numbers of B or CD5+ B cells but **augmented the ability of B cells to produce this response.** This was verified when a T cell-depleted B cell fraction or fluorescence-activated cell sorter purified CD5+ B cells from estrogen-treated mice proved more efficient in the production of APFC to Br-ME. These results suggest that the number of CD5+ B cells committed to produce autoantibodies to Br-ME is increased under the influence of estrogen. This is the first demonstration that estrogen can augment the production of natural autoantibodies in normal mice. The overall augmented humoral immune responses in females and the **B cell hyperactivity** in female predominant autoimmune diseases appears to be due to estrogen."

Cutis 1978 Mar;21(3):321-5. **Is vitamin E involved in the autoimmune mechanism?** Ayres S Jr, Mihan R

Free Radic Biol Med 2000 Jan 1;28(1):84-90. **Effect of exhaustive exercise on membrane estradiol concentration, intracellular calcium, and oxidative damage in mouse thymic lymphocytes.** Azenabor AA, Hoffman-Goetz L. "Intracellular Ca2+ levels were significantly higher in thymocytes of exercised compared with control mice ($p < .001$). There was a continuous flux of Ca2+ after exercise when cells were monitored in Ca2+ rich medium, with a significant influx between 160 and 200 sec ($p < .001$). Membrane bound estradiol was elevated in thymocytes of exercised compared to control mice ($p < .05$). Immediately after exercise there was a greater release of oxidative products by thymocytes in exhaustively exercised compared with control animals. There was also significant generation of lipid peroxide in thymus of exercised mice ($p < .001$). The findings suggest that exhaustive exercise may stimulate estradiol uptake by receptors on thymocytes, with a possible opening up of estradiol-receptor operated channels for Ca2+ entry into cells. This may have damaging effects on thymic lymphocytes by the triggering of oxidative reactions as determined by higher oxidative product release and greater generation of lipid peroxide."

Am J Pathol 1987 Jan;126(1):103-13 **Dietary fatty acid effects on T-cell-mediated immunity in mice infected with mycoplasma pulmonis or given carcinogens by injection.** Bennett M, Uauy R, Grundy SM. ". . . only mice on the POLY diet were significantly immunosuppressed, and only T-cell-mediated cutaneous sensitivity reactions were affected." "Deliberate infection with Mycoplasma pulmonis resulted in suppressed cutaneous T-cell responses in the POLY group of C3B6F1 mice, and aspirin partially reversed the immunosuppression." "It is tentatively concluded that diets rich in w-6 polyunsaturated diets, while not directly immunosuppressive, do predispose animals to suppression of certain T-cell-mediated immune responses. This immunosuppression can be "triggered" by infection and/or by exposure to carcinogens."

Trends Mol Med 2002 Oct;8(10):469-76. **Thymic regeneration: teaching an old immune system new tricks.** Berzins SP, Uldrich AP, Sutherland JS, Gill J, Miller JF, Godfrey DI, Boyd RL. **Recent studies in mice and humans show that the importance of the thymus extends well beyond the initial seeding of the peripheral T-cell pool.** Although peripheral homeostasis can maintain T-cell numbers, the thymus is the major,

if not the exclusive, source of new T-cell specificities. With age, thymus atrophy dramatically reduces the export of new T cells and predisposes an individual to impaired T-cell function, reduced T-cell immunity, and increased autoimmunity. Thymus atrophy is also the primary obstacle to restoration of the T-cell pool in the aftermath of HIV treatment or lymphoablative therapies. Here, we review thymus T-cell production, with particular attention to the factors that influence thymocyte export, and examine the impact that recent thymic emigrants have on the peripheral pool. In the future, thymic regeneration might become a feasible and potentially powerful approach to rejuvenating a depleted peripheral T-cell pool.

J Rheumatol 1990 Mar;17(3):311-7. **Sex hormone involvement in the induction of experimental systemic lupus erythematosus by a pathogenic anti-DNA idiotype in naive mice.** Blank M, Mendlovic S, Fricke H, Mozes E, Talal N, Shoenfeld Y "We found that injection of the pathogenic idiotype to BALB/c females and orchiectomized males treated with estrogen caused a rapid outburst of the disease 3 months after immunization, while nonestrogen treated mice developed the disease 5 months after immunization. The flare of SLE disease was characterized by raised levels of autoantibodies in the sera to dsDNA, histones, cardiolipin, Sm, RNP, SSA (Ro), SSB (La) and an emergence of high titers of mouse antibody carrying the 16/6 Id. These enhanced antibody levels were associated with an increase in erythrocyte sedimentation rate, proteinuria and leukopenia." "Our data demonstrate the importance of sex hormones on the induction of experimental SLE-like disease in mice with no genetic tendency to autoimmunity."

J Med 1980;11(2-3):81-105. **Serotonin and its precursors as modulators of the immunological responsiveness in mice.** Bliznakov EG. "The evidence of serotonergic-endocrine interrelations with regard to adrenal, thyroid, gonadal and prolactin functions is fast accumulating. Our study extends the importance of those interrelations to some functions of the immune system. **Multiple administration of 5-hydroxytryptamine(serotonin) or its precursor, 5-hydroxy-L-tryptophan(5-HTPH), produces marked depression of T cell dependent, humoral, hemolytic, primary immune response in mice. L-tryptophan, a more distant serotonin precursor, produces slight but significant depression of this immune response." "Administration of serotonin or 5-HTPH causes a marked reduction of the thymus weight. It is reasonable to postulate that the described effects result from the thymus involution which affects the T cell compartment of the immune system."** Since many clinically used drugs affect the serotonin metabolism, the clinical consequences of the resulting alteration of the immunological responsiveness should be considered."

J Steroid Biochem Mol Biol. 2002 Aug;81(4-5):309-17. **Differential activation of the IkappaBalpha and mouse mammary tumor virus promoters by progesterone and glucocorticoid receptors.** Deroo BJ, Archer TK. "To investigate how co-existing steroid receptors regulate gene transcription, we have compared two hormone-responsive promoters in T47D/A1-2 human breast cancer cells expressing both the GR and PR. The promoters chosen were those for the mouse mammary tumor virus (MMTV) and the gene for IkappaBalpha, the inhibitor of the ubiquitous transcription factor, nuclear factor kappa B (NFkappaB). Several differences between glucocorticoid and progestin activation of the IkappaBalpha and MMTV promoters were revealed. Both steroids activated the endogenous IkappaBalpha promoter, while only glucocorticoids activated a stably integrated MMTV promoter. In combination, progestins enhanced glucocorticoid activation of IkappaBalpha, but antagonized glucocorticoid activation of MMTV."

Fertil Steril 1991 Oct;56(4):718-24. **The relationship between in vitro fertilization and naturally occurring antibodies: evidence for increased production of antiphospholipid Autoantibodies.** Fisch B, Rikover Y, Shohat L, Zurgil N, Tadir Y, Ovadia J, Witz IP, Yron I OBJECTIVE: Assessment of possible effects of ovarian stimulation during in vitro fertilization (IVF) treatment cycles on circulating levels of antiphospholipid and antinuclear autoantibodies. DESIGN: The study was performed prospectively. Sera were obtained at three time points along IVF treatment cycle. Levels of autoantibodies directed against nuclear components, mitochondrial antigens, and phospholipids were determined using enzyme-linked immunosorbent assay. PATIENTS: Thirty-five patients, who underwent at least one previous IVF attempt, and 36 age- and sex-matched controls were analyzed. All participants were randomly selected. RESULTS: The mean levels of antiphospholipid (but not antinuclear) autoantibodies in sera from IVF-treated patients were found to be significantly higher than the corresponding values of the control group (for immunoglobulin [Ig]M isotype: anticardiolipin, antiphosphatidyl L-serine; for IgG isotype: anticardiolipin, antiphosphatidyl L-serine, and antiphosphatidylcholine; P less than 0.0001, assessed by Mann-Whitney test). The autoantibody levels remained more or less constant at different time points along the treatment cycle. No correlation with age and number of previous IVF cycles was demonstrated. CONCLUSIONS: Serum levels of antiphospholipid (but not antinuclear) autoantibodies increase after IVF treatment. Based on these preliminary data, it is not yet possible to estimate if the observed changes in autoantibody levels might have any future clinical influence on infertile patients undergoing IVF treatment. Comment in: Fertil Steril 1992 Oct;58(4):863-5.

Cell Mol Life Sci 1998 Oct;54(10):1076-82. **Regulation of B and T cell development by anterior pituitary hormones.** Foster M, Montecino-Rodriguez E, Clark R, Dorshkind K. Hormones produced by the anterior pituitary gland have been implicated in the regulation of primary lymphocyte development. In order to identify endocrine factors involved in that process, several strains of mice with genetic defects resulting in a selective impairment in the production of one or more anterior pituitary-derived hormones have been analysed. This study has resulted in the classification of endocrine hormones into the following four categories: (i) hormones such as prolactin with no apparent effects on primary lymphopoiesis; (ii) anabolic hormones such as growth hormone and insulin-like growth factor-I whose stimulatory effects on primary lymphopoiesis are non-lineage-specific and related to their actions as systemic mediators of growth and/or differentiation; (iii) hormones such as thyroid hormones that have an obligate role in primary B lymphopoiesis; and (iv) hormones such as oestrogens that act as negative regulators of lymphopoiesis.

J Clin Endocrinol Metab 1996 Mar;81(3):990-4. **Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy.** Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E, Pinchera A.

Schweiz Rundsch Med Prax 2001 Nov 1;90(44):1913-22. **[The environment and autoimmunity--from external causes to inner conflicts]** Gebbers JO. "Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. In most instances the events that initiate the immune response to self-molecules are unknown, but a number of studies suggest associations with environmental and genetic factors and certain types of infections. **The concordance of autoimmune diseases among identical twins is virtually always less than 50%, often in the 25-40% range.** This observation, as well as epidemic clustering of some autoimmune diseases following xenobiotic exposure, reinforces the thesis that autoimmune disease is secondary to both genetic and environmental

factors." "With these comments in mind it is important to note that there have been associations of a number of xenobiotics with human autoimmune disease, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, L-tryptophan, particulates, ultraviolet radiation, and ozone." "With the world-wide deterioration of the environment, this is a particular important subject for human health. This is best illustrated by the epidemics of eosinophilic myalgia syndrome with shared characteristics that occurred about 20 years ago. Another example is the toxic oil syndrome of Spain in 1981 involving cooking oil led to both acute and chronic disease as well as formation of auto-antibodies to collagen, DNA, and skeletal muscle. Currently the question is risen whether there is a link between environmental estrogens and autoimmune disorders, especially since these illnesses are reported possibly more frequent."

Biochem Pharmacol 2003 Apr 1;65(7):1027-34. **Broad-spectrum chemokine inhibitors (BSCIs) and their anti-inflammatory effects in vivo.** Grainger DJ, Reckless J.

Int J Immunopharmacol 1992 May;14(4):541-53. **Aromatase inhibitors regenerate the thymus in aging male rats.** Greenstein BD, de Bridges EF, Fitzpatrick FT.

Clin Exp Immunol 1993 Jun;92(3):432-6. **Pinealectomy ameliorates collagen II-induced arthritis in mice.** Hansson I, Holmdahl R, Mattsson R.

Physiol Behav 1999 Dec 1-15;68(1-2):169-74. **Effect of estradiol and exercise on lymphocyte proliferation responses in female Mice.** Hoffman-Goetz L. "This study investigated the effect of estradiol exposure and physical exercise on lymphocyte proliferation responses to T and B cell mitogens in female mice." **"In the thymus, there was a significant reduction of proliferation to ConA in the Ovx + E2 animals** relative to the other conditions at both concentrations of mitogen. At 1.0 microg/mL concentration, there was a significant interaction of hormone and exercise treatments. Sham (control) mice given exercise had a higher proliferation response relative to sedentary counterparts, whereas E2 mice did not differ in proliferation responses, irrespective of exercise condition. In the spleen, exposure to high concentrations of estradiol was associated with reduced proliferation responses to both mitogens; there were, however, no main or interaction effects of exercise. These results suggest that high levels of estradiol exposure following ovariectomy in mice significantly reduces lymphocyte blastogenesis responses, and that thymic immunomodulation after acute exercise is masked by the hormonal effect."

J Neuroimmunol 2003 Jan;134(1-2): 25-34. **Autoreactive T cells promote post-traumatic healing in the central nervous system.** Hofstetter HH, Sewell DL, Liu F, Sandor M, Forsthuber T, Lehmann PV, Fabry Z. In general, autoimmune responses are considered harmful to the host. In the best-defined model of autoimmune disease, murine experimental allergic encephalomyelitis (EAE), for example, brain-protein-specific autoimmune responses of both major classes, type-1 and type-2, have been implicated in causing brain pathology. We induced type-1 and type-2 autoimmunity to myelin oligodendrocyte protein (MOG) in C57.BL/6 mice. Instead of using pertussis toxin (PTX) to open the blood-brain barrier (BBB), which is the classic procedure, we set an aseptic cerebral injury (ACI) to see what the consequences of pre-primed, autoreactive type-1 and type-2 memory T cells gaining access to the brain in the course of sterile tissue injury would be. **Neither of these autoimmune response types induced pathology; on the contrary, both accelerated re-vascularization and post-traumatic healing.** The data suggest that induction of either type-1 or type-2 autoimmune responses is not inherently noxious to the host, but can have beneficial effects on tissue repair. Autoimmune pathology may develop only if molecules of microbial origin such as pertussis toxin additionally induce the "infectious nonself/danger" reaction in the antigen-presenting cells (APC) of the target organ itself.

Arch Histol Cytol 1997 Mar;60(1):65-78. **Glucocorticoid-induced thymocyte death in the murine thymus: the effect at later stages.** Ishii T, Nakamura M, Yagi H, Soga H, Kayaba S, Gotoh T, Satomi S, Itoh T. "We report here on kinetics of glucocorticoid-induced murine thymocyte death in vivo by the TUNEL method. TUNEL-positive cells were observed as early as at 2 h after intraperitoneal injection of glucocorticoid." "At 6 to 8 h after the injection, the number of phagocytosed thymocytes per individual macrophage had reached its maximum, and at 8 to 12 h many ruptured macrophages ingesting too many dying thymocytes became noticeable. During the process, no additional macrophages appeared to be mobilized to the thymus. At 6 to 8 h after the injection, however, coincidentally with the fact that macrophages had become unable to further ingest dying lymphocytes, dead cells were left unphagocytosed, and ultimately became "free" positive cells, probably due to some proteolytic process ongoing within the thymus. As late as at 12 h, morphological examination revealed that epithelial cells seemed to begin engulfing thymocytes, almost simultaneously with the start of rupture of the macrophages due to the ingestion of too many thymocytes." "Altogether, these results suggest that: 1) even though thymocytes were exposed to glucocorticoid in vivo, most of them were not TUNEL-positive unless they were phagocytosed; 2) even after most macrophages had ingested too many cells at later stages, macrophages in other locations did not migrate to the thymus; and finally, 3) deletion of damaged thymocytes was also carried out by thymic epithelial cells, though not frequently, at around 12 h and later."

Rinsho Shinkeigaku 1993 Sep;33(9):995-7. **[A case of Hashimoto's encephalopathy with a relapsing course related to menstrual cycle]** Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Shoji S. A case of 43-year-old woman with Hashimoto's encephalopathy who experienced three relapses closely associated with the menstrual cycle is reported. In April 1992, she began to experience occasional tremors in her arms. Three months later, she experienced a generalized seizure and was transferred to our hospital. Hashimoto's thyroiditis was diagnosed on the basis of high thyroid microsomal titer and mild hypothyroidism. Neurological findings in admission included action tremor in both hands, myoclonus in all extremities, cerebellar ataxia, confusion, and hyperreflexia. Cerebrospinal fluid showed elevated protein level without pleocytosis. Electroencephalogram showed diffuse slowing and magnetic resonance imaging of brain was normal. Hashimoto's encephalopathy was diagnosed from these findings. **These episodes of remission and exacerbation were observed during the admission. Her symptoms started at ovulation, worsened during the luteal phase, and improved when menstruation started. After the third relapse, she was treated with oral thyroxine for hypothyroidism and with an estrogen and progesterone combination to regulate the menstrual cycle. Her thyroid function gradually became euthyroid and she did not experience any subsequent relapses. The relation between the relapsing course and menstrual cycle suggests that the periodic alteration of gonadotrophic and/or gonadal hormones or the menstrual regulating center itself in the brain may be an important factor of pathogenetic mechanism of the disorder.**

Transplantation 1989 Jul;48(1):98-102. **Enhancement of immunosuppression by substitution of fish oil for olive oil as a vehicle for cyclosporine.** Kelley VE, Kirkman RL, Bastos M, Barrett LV, Strom, T.B.

Berl Munch Tierarztl Wochenschr 1992 Mar 1;105(3):81-85. **[Modification of lymphoblastic transformation by estradiol, progesterone and corticosterone in vitro].** Kuhn V, Hardegg W "In conclusion, corticosterone, E2 and progesterone showed a dose-dependent influence on lymphoblast transformation of thymocytes and splenocytes and progesterone had opposite effects on corticosterone-induced suppression of blastogenesis in rat lymphocytes, especially in thymocytes."

J Immunol 1990 Mar 15;144(6):2147-51. **The nonobese diabetic mouse model. Independent expression of humoral and cell-mediated autoimmune features.** Lehuen A, Bendelac A, Bach JF, Carnaud C. "Altogether, these results suggest that NOD mice, like other autoimmune strains, **suffer from a genetically inherited defect of B cell regulation resulting in the hyperproduction of natural autoantibodies."**

Int J Immunopharmacol 1984;6(4):287-97. **Mechanisms of estrogen-induced myelotoxicity: evidence of thymic regulation.** Luster MI, Boorman GA, Korach KS, Dieter MP, Hong L. "Mice exposed to pharmacological levels of steroidal and nonsteroidal estrogens including alpha-dienestrol, 17 beta-estradiol, and diethylstilbestrol **demonstrate bone marrow hypocellularity, and decreased numbers of pluipotent hemopoietic stem cells.** Hormones with little estrogenic activity including testosterone and progesterone failed to induce myelotoxicity as did nonestrogenic metabolites of DES." "One of these mechanisms is mediated through the thymus since surgical thymectomy abolished the ability of estrogens to suppress CFU proliferation." "That the initial events in estrogen-induced myelotoxicity may be mediated through a receptor

mechanism was suggested by the ability of antiestrogens to induce antagonism when administered prior to estradiol and the presence of estrogen binding components in lymphoreticular tissues including the thymus and bone marrow. These studies suggest that reduced CFU kinetics observed following estrogen exposure is, in part, due to alterations in regulatory factors produced by thymic epithelial cells in response to a specific estrogen stimulus."

Fertil Steril 1983 Apr;39(4):485-489. **The effect of aqueous progesterone on operative adhesion Formation.** Maurer JH, Bonaventura LM "Progesterone (P) has been shown to have antiinflammatory and immunosuppressive properties. This study was designed to evaluate these effects on operative adhesion formation." Forty guinea pigs received standardized injuries to their uterine horns. Four groups were examined. Normal saline was used as an irrigant in the first, or control, group. Aqueous P (50 mg or 1 ml) was dripped over the injured site and instilled intraperitoneally in the second group. The third group received intramuscular aqueous P (3.3 mg/kg body weight) 1 day postoperatively, the day of surgery, and either 6 or 13 days postoperatively until reexploration. In the fourth group 1 ml of 32% dextran 70 (Hyskon) was administered in the same manner as aqueous P in the second group. The animals in all groups were reexplored 1 or 2 weeks after the initial surgical procedure, and the adhesions were scored. Adhesion formation was significantly reduced (P less than 0.001) in all treatment groups when compared with the control group."

Int J Immunopharmacol 2000 Nov;22(11):955-65. **Progesterone inhibits glucocorticoid-induced murine thymocyte apoptosis.** McMurray RW, Wilson JG, Bigler L, Xiang L, Lagoo A. "Sex and sex hormones modulate immune development and responses. A primary target of their effects is the structure and cellularity of the thymus; therefore, we examined the effects of sex and sex steroids on thymocyte apoptosis." **"Both estrogen and testosterone increased in vitro thymocyte apoptosis. In contrast, progesterone not only inhibited spontaneous in vitro thymocyte apoptosis, but also prevented in vitro glucocorticoid-induced apoptosis. Progesterone administration also suppressed glucocorticoid-induced in vivo thymocyte apoptosis. These results suggest that anti-apoptotic effects of progesterone may influence T cell development and subsequent immune responses."**

J Neuroimmunol 1997 May;75(1-2):1-8. **Inhibitory effect of pregnancy on stress-induced immunosuppression through corticotropin releasing hormone (CRH) and dopaminergic systems.** Nakamura H, Seto T, Nagase H, Yoshida M, Dan S, Ogino K "Decreases in splenic NKCA, corticotropin releasing hormone (CRH) in the hypothalamus, and increases in progesterone (P), beta-endorphin (beta EP), and dopamine (DA) metabolic ratios in the frontal cortex and nucleus accumbens produced by stress were recognized in the virgin rats, but not in the pregnant rats. Pregnancy reduced splenic NKCA in rats without stress, but elevated it in the rats exposed to stress with a duration of 180 min. These findings suggest inhibitory Effects of pregnancy on stress-induced immunosuppression and neuroendocrine changes, thereby promoting homeostasis in the neuroendocrine-immune system against stress. Such enhanced homeostasis associated with pregnancy seemed to be mediated by the activation of placental P and placental or pituitary beta EP in cooperation with mesocortical and mesolimbic DA systems and hypothalamic CRH."

Toxicology 2001 May 28;163(1):49-62. **Evidence for estradiol-induced apoptosis and dysregulated T cell maturation in the thymus.** Okasha SA, Ryu S, Do Y, McKallip RJ, Nagarkatti M, Nagarkatti PS. "The thymocytes from E2-treated mice when cultured in vitro for 24h, showed increased levels of apoptosis when compared to controls." "However, the total cellularity of all T cell subsets in the thymus was decreased following E2 treatment." "These data therefore confirmed that the thymocytes were indeed undergoing apoptosis following E2 treatment. Together, our studies suggest for the first time that estrogen may induce thymic atrophy by triggering apoptosis."

Am J Physiol Endocrinol Metab 2002 Nov;283(5):E909-16. **Endotoxemia reduces skeletal muscle protein synthesis in neonates.** Orellana RA, O'Connor PM, Nguyen HV, Bush JA, Suryawan A, Thivierge MC, Fiorotto ML, Davis TA. **"Protein synthesis in skeletal muscle is reduced by as much as 50% as early as 4 h after a septic challenge in adults."** "These findings suggest that, when substrate supply is maintained, skeletal muscle protein synthesis in neonates compared with adults is relatively resistant to the catabolic effects of sepsis."

Exp Neurol 1987 Mar;95(3):639-51. **Immunocomplexes in rat and rabbit spinal cord after injury.** Palladini G, Grossi M, Maleci A, Lauro GM, Guidetti B. "The possibility that, following a major lesion of the central nervous system, a humoral immune response could be evoked with formation of immune complexes "in situ" was investigated. For this purpose, an immunohistochemical study on rabbit and rat spinal cord at different times after surgical transection was carried out." "The results showed in the rabbit the absence of antibodies to neural antigens before surgical injury and its appearance within a few days after surgery. On the other hand, in the rat, even before the injury, we found antibodies to neural tissue which decreased in the first few hours after injury, and returned to control values during successive days." "The possible role of this immune response in the failure of axonal regeneration in mammalian spinal cord is briefly discussed."

FEBS Lett 1997 Apr 7;406(1-2):136-8. **Age-dependent decline in the cytochrome c oxidase activity in rat heart mitochondria: role of cardiolipin.** Paradies G, Ruggiero FM, Petrosillo G, Quagliariello E. "Cardiolipin is a major mitochondrial membrane lipid and plays a pivotal role in mitochondrial function. We have recently suggested a possible involvement of this phospholipid in the age-linked decline of cytochrome c oxidase activity in rat heart mitochondria [G. Paradies et al. (1993) Arch. Gerontol. Geriatr. 16, 263-272]." "We demonstrate that the lower cytochrome c oxidase activity in heart mitochondria from aged rats can be fully restored to the level of young control rats by exogenously added cardiolipin. No restoration was obtained with other phospholipids or with peroxidized cardiolipin. Our data support a key role for cardiolipin in the age-linked decline of rat heart mitochondrial cytochrome c oxidase activity."

Arch Biochem Biophys 1991 Feb 1;284(2):332-7. **Effect of aging on the activity of the phosphate carrier and on the lipid composition in rat liver mitochondria.** Paradies G, Ruggiero FM. "The effect of aging on the activity of the phosphate carrier and on the lipid composition in rat liver mitochondria has been investigated. It was found that the rate of phosphate transport in mitochondria from aged rats (28 months old) is significantly reduced (around 40%) compared to that obtained in mitochondria from young control rats (5 months old)." "The hepatic mitochondrial lipid composition is altered significantly in aged rats: the total cholesterol increases (31%), the phospholipids decrease (12%), and the cholesterol/phospholipid molar ratio increases (44%). Among the phospholipids cardiolipin shows the greatest alteration (30% decrease with age). Alterations were also found in the pattern of fatty acids. The age-related decrement in the activity of the phosphate carrier appears to be dependent on changes in the lipid domain surrounding the carrier protein molecule in the mitochondrial membrane."

J Exp Med 1978 Jun 1;147(6):1568-83. **Effect of castration and sex hormone treatment on survival, anti-nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice.** Roubinian JR, Talal N, Greenspan JS, Goodman JR, Siiteri PK."Mice receiving androgen showed improved survival, reduced anti-nucleic acid antibodies, or less evidence of glomerulonephritis as determined by light, immunofluorescent, and electron microscopy. By contrast, opposite effects were observed in castrated mice receiving estrogen. Intact male NZB/NZW F1 mice received androgen implants at 8 mo, an age when they develop an accelerated autoimmune disease associated with a decline in serum testosterone concentration. Such treated mice had improved survival and reduced concentrations of antibodies to DNA and to polyadenylic acid (Poly A)."

J Clin Invest 1977 Jun;59(6):1066-70. **Androgenic hormones modulate autoantibody responses and improve survival in murine lupus.** Roubinian JR, Papoian R, Talal N

Int J Immunopharmacol 1999 Dec;21(12):861-8. **Inhibitory effect of natural and environmental estrogens on thymic hormone production in thymus epithelial cell culture.** Sakabe K, Okuma M, Karaki S, Matsuura S, Yoshida T, Aikawa H, Izumi S, Kayama F. "The production of thymosin-alpha 1 by TECs was significantly inhibited by increasing concentrations of 17beta-estradiol (natural estrogen) over 3 x 10(-11) M, genistein (phytoestrogen) over 3 x 10(-9) M, coumestrol (phytoestrogen) over 3 x 10(-9) M, alpha-zearalanol (livestock anabolic) over 3 x 10(-7) and bisphenol-A (plastic) over 3 x 10(-6) M." "The above results clearly indicate that natural and environmental estrogens directly modulate TECs to produce thymic hormone probably through an estrogen receptor mechanism."

J Immunol 1994 Mar 1;152(5):2586-95. **Ionizing radiation and autoimmunity. Induction of autoimmune disease in mice by high dose fractionated total lymphoid irradiation and its prevention by inoculating normal T cells.** Sakaguchi N, Miyai K, Sakaguchi S. "Ionizing radiation can functionally alter the immune system and break self-tolerance."

Immunol Invest 1992 Feb;21(1):1-10. **Studies on the immunosuppressive role of steroid hormones during Pregnancy.** Saleem MA, Jha P, Buckshee K, Farooq A

Science 1988 May 20;240(4855):1032-3. **Essential fatty acid depletion of renal allografts and prevention of rejection.** Schreiner GF, Flye W, Brunt E, Korber K, Lefkowith JB "Kidneys subjected to EFAD and thus depleted of resident Ia-positive macrophages survived and functioned when transplanted across a major histocompatibility antigen barrier in the absence of immunosuppression of the recipient. Control allografts were rejected promptly. Allografts from donors subjected to EFAD normalized their lipid composition and were repopulated with host macrophages by 5 days. Administration of Ia-positive cells at the time of transplantation established that the resident leukocyte depletion induced by EFAD was responsible for the protective effect."

Microsc Res Tech 1997 Aug 1;38(3):216-26. **Thymic microenvironment at the light microscopic level.** Schuurman HJ, Kuper CF, Kendall MD. "The thymus is a primary lymphoid organ that serves the immune system by providing an optimal microenvironment for developing T cells to rearrange the genes encoding the T-cell receptor and to undergo positive and negative selection in shaping the peripheral T-cell repertoire." "Bone marrow-derived interdigitating cells and macrophages are the main accessory cell populations. The epithelium, interdigitating cells, and macrophages each contribute to the T-cell selection process."

J Immunol 1979 Jun;122(6):2541-7. **Natural killer cells, bone, and the bone marrow: studies in estrogen-treated mice and in congenitally osteopetrotic (mi/mi) mice.** Seaman WE, Gindhart TD, Greenspan JS, Blackman MA, Talal N **"Mice lose natural killer cells after 6 weeks of treatment with 17 beta-estradiol."** "From these observations, we conclude that estrogens do not reduce natural killer cells simply by reducing the volume of bone marrow. Estrogens may instead have an effect on bone marrow cells that leads both to osteoproliferation and to a deficiency of marrow-dependent cells."

J Immunol 1978 Dec;121(6):2193-8. beta-**Estradiol reduces natural killer cells in mice.** Seaman WE, Blackman MA, Gindhart TD, Roubinian JR, Loeb JM, Talal N. "Four to 6 weeks of estrogen administration caused a substantial reduction in natural killer cell activity in the spleens from mice of either sex. Androgen (5alpha-dihydrotestosterone) did not." "The effects of estradiol were not dependent on the thymus, since estradiol reduced natural killing in mice that had been neonatally thymectomized. After removal of the estrogen implant, natural killing recovered over a period of 8 weeks. The loss of natural killing may reflect a loss of bone marrow secondary to estrogen-induced osteosclerosis."

Lupus. 2004;13(4):217-22. **Possible mechanisms of gender bias in SLE: a new hypothesis involving a comparison of SLE with atopy.** Sekigawa I, Naito T, Hira K, Mitsuishi K, Ogasawara H, Hashimoto H, Ogawa H. **"Estrogens seem to play an important role in the overexpression of endogenous autoantigens, such as human endogenous retroviruses (HERV),** and this may be related to the existence of a gender bias in the incidence of SLE but not atopy."

Ann N Y Acad Sci 1999 Jun 22;876:159-63. **Association between anticardiolipin antibody positivity and increased 17-beta-estradiol levels in premenopausal women with rheumatoid arthritis.** Seriolo B, Accardo S, Garnero A, Fasciolo D, Cutolo M

Clin Immunol Immunopathol 1983 Mar;26(3):361-9. **Effects of castration and sex hormones on immune clearance and autoimmune disease in MRL/Mp-lpr/lpr and MRL/Mp-+/+ mice.** Shear HL, Wofsy D, Talal N. "The clearance of erythrocytes sensitized with IgG was studied in MRL/Mp-lpr/lpr (MRL-lpr) and MRL/Mp-+/+ (MRL-+/+) mice, which spontaneously develop autoimmune disease." "Androgen treatment improved clearance in MRL-+/+ mice but not in MRL-lpr mice, even though autoantibody levels, renal function, and survival were improved. These results suggest that the beneficial effects of androgen on autoimmune disease are not due solely to improved clearance of immune complexes."

Kidney Int 1992 May;41(5):1245-53. **Essential fatty acid deficiency normalizes function and histology in rat nephrotoxic nephritis.** Takahashi K, Kato T, Schreiner GF, Ebert J, Badr KF "The central lipid abnormality in essential fatty acid deficiency (EFAD) is the lack of availability of arachidonic acid. To examine the role of total eicosanoid's biosyntheses in the pathology and pathophysiology of glomerulonephritis, EFAD was induced in weanling rats, which were then subjected to antiglomerular basement membrane antibody (NTS)-induced injury in adulthood." "Two hours post-NTS, and despite the occurrence of proteinuria in both EFAD and STD animals, glomerular dynamics were essentially normal in EFAD rats, whereas STD animals had reduced values for glomerular filtration rate (GFR) and renal plasma flow rate (RPF). At two weeks, severe histologic changes were observed in STD animals including mesangial and stalk hypercellularity, moderate sclerosis, and interstitial nephritis, coupled with heavy proteinuria and reduced GFR and RPF. In dramatic contrast, EFAD rats displayed totally normal glomerular structures and functions. In parallel, glomerular generation rates of prostaglandin E2 and thromboxane A2 were suppressed markedly in EFAD rats. **Thus, EFAD confers complete protection against the histopathologic and functional sequelae of immune-initiated injury in the glomerulus.** The data suggest that the initial wave of complement-induced neutrophil infiltration (with resultant proteinuria) is not sufficient to perpetuate injury into the more destructive chronic phases."

The New England Journal of Medicine Volume 326:513-518 February 20, 1992 Number 8. **Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis.** N Takasu, T Yamada, M Takasu, I Komiya, Y Nagasawa, T Asawa, T Shinoda, T Aizawa, and Y Koizumi. "Hypothyroidism may result from the production of antibodies that block the actions of thyrotropin." "Thyrotropin-blocking antibodies were detected in 9 percent of the patients with goitrous autoimmune thyroiditis and in 25 percent of those with atrophic autoimmune thyroiditis. Among the 21 patients studied serially while receiving levothyroxine, thyrotropin-blocking antibodies disappeared in 15 (group 1), 7 of whom had goiter initially, and persisted in 6 (group 2), none of whom had goiter initially. Levothyroxine therapy was subsequently discontinued in these 21 patients. Six of those in group 1 (four with goiter) remained euthyroid (mean follow-up after discontinuation of therapy, 2.1 years), and nine became hypothyroid again within 3 months. All six patients in group 2 remained hypothyroid." "Hypothyroidism in some patients with autoimmune thyroiditis may be due to thyrotropin-blocking antibodies. The production of thyrotropin-blocking antibodies may subside, producing remissions of hypothyroidism. Chronic autoimmune thyroiditis may therefore cause transient as well as permanent hypothyroidism."

J Rheumatol 1987 Jun;14 Suppl 13:21-5 **"Interleukin 2, T cell receptor and sex hormone studies in autoimmune mice."** Talal N, Dang H, Ahmed SA, Kraig E, Fischbach M. "Systemic lupus erythematosus (SLE) is a disease of immune dysregulation in which B cell hyperactivity and T cell deficiency are important characteristics. Sex factors also play a major role in the pathogenesis based on the physiologic effects of estrogen in promoting immunologic hyperactivity." "This aberrant T cell receptor might be explained by a defect in glycosylation. The administration of estrogen to pregnant mice late in gestation results in offspring with a permanently altered immune system. These mice develop features of autoimmunity similar to those that occur spontaneously in genetically susceptible autoimmune mice. This phenomenon may have etiopathological significance for familial SLE.

Isr J Med Sci 1988 Dec;24(12):725-8. **Sex hormones, CD5+ (Lyl+) B-cells, and autoimmune diseases.** Talal N, Ahmed SA

Ann N Y Acad Sci 1986;475:320-8 **Hormonal approaches to immunotherapy of autoimmune disease.** Talal N, Ahmed SA, Dauphinee M

Clin Rheum Dis 1982 Apr;8(1):23-8. **Sex hormones and modulation of immune response in SLE.** Talal N. Clearance of sensitized erythrocytes in NZB/NZW mice. Effects of castration and sex hormone treatment. Shear HL, Roubinian JR, Gil P, Talal N. The clearance of particulate immune complexes consisting of erythrocytes sensitized with IgG or complement was investigated in (NZB x NZW)F1 (B/W) mice. Treatment of castrated B/W mice with androgen or estrogen was able to modulate this clearance. Young (3-month-old) male and female B/W mice cleared IgG-sensitized mouse erythrocytes rapidly, whereas older males (13 months) and females (7 months) showed a marked impairment in their ability to clear these cells. In addition, erythrocytes sensitized **with complement in the absence of antibody were cleared within 5 min in**

young B/W mice. Older mice showed a greater and more rapid clearance rate of these cells. Castrated female B/W mice treated with androgen implants from three weeks of age showed improved clearance of IgG-sensitized erythrocytes at 7 months, whereas **estrogen-treated male mice showed delayed clearance. These results suggest an age-dependent defect** in the clearance of IgG-sensitized particles, perhaps due to diminished levels of serum complement and/or saturation of Fc receptors. In addition, there is an alteration in the clearance of complement-sensitized erythrocytes which may be related to changes in macrophage activity or enzyme inactivators of C3 and C4. The possible mechanisms responsible for the hormonal modulation of clearance are discussed in relation to the known ability of these hormones to influence autoimmune diseases.

Arthritis Rheum 1981 Aug; 24(8):1054-6 **Sex steroid hormones and systemic lupus erythematosus.** Talal N.

Med Cutan Ibero Lat Am 1980;8(1-3):15-21. **[Postovulation dermatitis (dermatitis caused by progesterone)]** Torras H, Ferrando J, Mallolas J. Postovulation Dermatitis is a frequent clinical picture although it is not well known. Clinically a polymorphous eruption appears between than 8 or 10 day before menses. The Authors report three cases in which an complete immunological investigation was performed. They conclude that there is no objective evidence of the autoimmune pathogeny of this picture in spite of the clinical relationship between the dermatitis and the ovulation. Therefore they suggest that diseases should be described as "Postovulation Dermatitis" instead "Autoimmune Progesterone Dermatitis".

J Endocrinol Invest 1993 Sep;16(8):619-24. **Hormonal pattern in women affected by rheumatoid arthritis.** Valentino R, Savastano S, Tommaselli AP, Riccio A, Mariniello P, Pronesti G, De Divitiis PM, Lombardi G. **"We have previously reported the presence of progesterone (P) deficiency in female patients with thyroid and ovarian autoimmune disease."** "In this context, the hormonal profile in 9 women with rheumatoid arthritis (RA) and in 9 age-matched ealthy women, were evaluated to verify the presence of a steroid hormone secretion impairment in a systemic autoimmune disease, further supporting our hypothesis of P deficiency involvement. P and androgen plasma levels, in the luteal phase, were significantly lower ($p < 0.05$ and 0.005, respectively) in RA patients than in the control group...." "Moreover, despite normal cortisol values, corticosterone (B) plasma levels were significantly higher in the RA patients ($p < 0.01$ and 0.05 in follicular and luteal phase, respectively). Therefore, our present data confirm the androgen deficiency in patients with a systemic autoimmune disease, such as RA and support the immunomodulator effect of P." "In conclusion, in addition to androgens, the immunomodulator role of P should also be taken into account in the pathogenesis of the systemic autoimmune disease."

Endocrinology 1994 Dec; 135(6): 2615-22. **"17 beta-estradiol, but not 5 alpha-dihydrotestosterone, augments antibodies to double-stranded deoxyribo- nucleic acid in nonautoimmune C57BL/6J mice."** Verthelyi D, Ahmed SA "In this study, we investigated the influence of gender and sex hormones on the development of antibodies to double-stranded DNA in nonautoimmune C57BL/6J mice." "In summary, our findings suggest that estrogen, but not dihydrotestosterone, promotes anti-dsDNA antibodies in normal mice."

Int Immunopharmacol 2001 Jun;1(6):983-93. **Sex hormones as immunomodulators in health and disease.** Verthelyi D. **"Studies in normal mice show that estrogen treatment induces polyclonal B cell activation with increased expression of autoantibodies characteristic of autoimmune diseases.** Several mechanisms appear to contribute to the break in tolerance and the increase in plasma cell activity including a reduction of the mass of the bone marrow and the thymus, the emergence of sites of extramedullary hematopoiesis and altered susceptibility of B cells to cell death. In addition, sex hormone levels in both humans and experimental models correlated with the activity of their cytokine-secreting cells indicating that sex hormones influence the cytokine milieu and suggesting that altered sex hormonal levels in autoimmune patients contribute to the skewed cytokine milieu characteristic of systemic lupus erythematosus (SLE)."

Cell Immunol 1998 Nov 1;189(2):125-34. **"Estrogen increases the number of plasma cells and enhances their autoantibody production in nonautoimmune C57BL/6 mice."** Verthelyi DI, Ahmed SA "In this study, by employing ELIspot, image cytometry, flow cytometry, cytology, and ELISA, we show that long-term exposure of normal mice to estrogen activates B cells to produce higher numbers of not only immunoglobulin-producing cells, but also autoantibody-producing cells. **Estrogen promoted a decrease in B220(+) splenic lymphocytes, but resulted in a 10-fold increase in plasma cells.** Further, the output of immunoglobulins including autoantibodies from individual plasma cells from estrogen-exposed mice was markedly increased, suggesting B cell hyperactivity. Importantly, our findings show that treatment of normal mice, solely with estrogen, can override B cell tolerance and promote autoreactive B cells in normal individuals."

Immunol Rev 1989 Aug;110:173-85. **Peripheral T cells select the B-cell repertoire in old mice.** Weksler ME, Russo C, Siskind GW. "These studies have shown that the alterations in the repertoire of antibody produced by old mice is not due to an intrinsic defect in the bone marrow or in the B-lymphocyte population arising from the bone marrow but rather to a selective downregulation by auto-anti-idiotypic antibody and idiotype-anti-idiotype interactions, shifting the idiotype distribution in the peripheral B-cell population." "The overall shift may be described as a decreased reactivity to foreign antigens and a complementary increase in reactivity with self antigens."

Proc Natl Acad Sci U S A 2002 May 28;99(11):7616-21. **The phytoestrogen genistein induces thymic and immune changes: a human health concern?** Yellayi S, Naaz A, Szewczykowski MA, Sato T, Woods JA, Chang J, Segre M, Allred CD, Helferich WG, Cooke PS. "Use of soy-based infant formulas and soy/isoflavone supplements has aroused concern because of potential estrogenic effects of the soy isoflavones genistein and daidzein. Here we show that s.c. genistein injections in ovariectomized adult mice produced **dose-responsive decreases in thymic weight of up to 80%.** Genistein's thymic effects occurred through both estrogen receptor (ER) and non-ER-mediated mechanisms, as the genistein effects on thymus were only partially blocked by the ER antagonist ICI 182,780. **Genistein decreased thymocyte numbers up to 86% and doubled apoptosis, indicating that the mechanism of the genistein effect on loss of thymocytes is caused in part by increased apoptosis." "Critically, dietary genistein at concentrations that produced serum genistein levels substantially less than those in soy-fed infants produced marked thymic atrophy.** These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants."

Life Sci 2000 Mar 3;66(15):1451-9. **Supraphysiological level of estrogen exposure in vivo increases lymphoid cell death in mice.** Zajchowski S, Hoffman-Goetz L. "These results suggest that supraphysiological levels of estrogen in vivo induce damage in lymphoid cells; however, the impact of estrogen associated lymphoid tissue damage on specific immune functions remains to be determined."

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Ray Peat's Newsletter

"The problems we face today cannot be solved by the minds that created them" Albert Einstein

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"In the last few months cardiac hormones (i.e. atrial natriuretic peptides) have been shown for the first time to decrease the size of infarcts after acute myocardial infarctions and to cure 80% of human pancreatic cancers and two-thirds of human breast cancers in athymic mice without any surgery. Even the human pancreatic cancers that were not cured had their volume decreased to less than 10% with each of four cardiac hormones and with vessel dilator to less than 2% compared to untreated animals. None of the treated human pancreatic cancer animals died of cancer – they lived a normal lifespan and died of old age."

"In the past year the mechanism of how cardiac hormones cure cancer(s) has been largely elucidated in cancer cells: They target the RAS/RAF-MEK 1/2-ERK 1/2 kinase cascade by inhibiting up to 98% of the activation (phosphorylation) of both MEK 1/2 and ERK 1/2 and block completely the stimulation of ERK by mitogens such as epideral growth factor resulting in decreased DNA synthesis within the nucleus of the cancer cell.

Cardiac hormones (i.e. atrial natriuretic peptides) consist of a family of peptides which are synthesized and then stored as three different prohormones, i.e., 126 amino acid (a.a.) atrial natriuretic peptide (ANP), 108 a.a. brain natriuretic peptide (BNP) and 103 a.a. C-natriuretic peptide (CNP) prohormones. Within the 126 a.a. ANP prohormone are four peptide hormones i.e. ANP, long acting natriuretic peptide (LANP), vessel dilator, and kaliuretic peptide with blood pressure lowering, natriuretic, diuretic and/or kaliuretic (i.e., potassium excreting) properties."

David Vesely, 2008

Peptides, coherent adaptation, and some terminal diseases: *The roles of thyroid, progesterone, calcium, salt--issues of energy and inflammation; towards an organismic paradigm for medicine*

In the last 50 years, huge numbers of people have probably suffered needlessly and died prematurely because of a mistaken bio-medical ideology. Much of that ideology has been deliberately imposed by a corrupt drug industry, which effectively controls the regulatory agencies, major medical journals and texts, and the way the mass media treat scientific ideas.

Scientific reductionism fosters specialization, and specialization leaves the "big picture" susceptible to manipulation by those with financial and political power.

The practice of medicine is still based on mechanistic biological doctrines, but some of the coherent holistic approaches that disappeared after the second world war are being vindicated by recent research.

In treating heart disease, it's common to prescribe one drug to modify the heart's contractions, another drug to modify the kidneys' handling of water and sodium, another drug that modifies the tension of the blood vessels, and a drug to inhibit blood clotting. In treating cancer, drugs to kill tumor cells are often combined with drugs to treat the side effects of the toxic drugs, and other drugs to treat symptoms produced by the cancer. Each drug has its particular "indications," and the whole process seems to be logical and rational, as long as the doctor participates in the mechanistic culture that describes the organism and each drug's effect on the organism.

Epilepsy, diabetes, osteoporosis, depression, boils, arthritis, insomnia, etc., all have their special mechanisms and special drugs.

When a practicing physician is confronted by a patient who is trying to think about the problem coherently, in terms of things that were known in 1940 or that have been recently discovered, it's extremely unlikely that the physician will take the time, or have the mental flexibility, to consider the patient's perspective.

There is nothing in the present medical culture that would allow a physician to consider that a common substance such as progesterone, or thyroid, or calcium, or sugar, might be able to prevent or alleviate or cure some or all of the conditions mentioned above. But there are some clearly established facts that have the potential of radically changing medical culture.

The idea of cell renewal ("tissue streaming") with coordinated multiplication of stem cells and safe dissolution (apoptosis) and recycling of mature cells has now reached mainstream biology, despite some occasional lip-service to the "Hayflick limit," which submerged the idea of continuous tissue renewal for 40 years. The idea of tissue-specific regulators of cell division (e.g., W.S. Bullough's chalones) was incompatible with the Hayflick doctrine that mature cells were incapable of dividing, and with the cancer doctrine, that only genetic mutant cells were able to continue dividing beyond the Hayflick limit of 50 divisions. But now, there is great interest in studying the many specific and general factors that regulate stem cells, differentiation, and apoptosis in the mature animal.

Some of these basic regulatory systems that have been ignored for so long turn out to be processes that we have in common with all forms of life.

Every cell contains proteolytic enzymes that break down enzymes and other proteins as new proteins are made. These changes allow the cell to adapt to changes in its environment, such as different energy sources. During stress, these enzymes are activated so that new systems can be quickly formed to meet the stress. When the stress is so intense that the cell is unable to adapt, enzymes of this sort break down the cell's structure, and the synthesis of new proteins stops, causing the cell to decompose in an orderly way. More intense and sudden stress can cause a less orderly kind of cellular death, but the proteolytic enzymes participate in that kind of dissolution too, though the peptide fragments produced are different.

Bacteria growing in colonies function in some ways like multicellular organisms, and the adaptive processes, including cell dissolution when the supply of food is depleted, allow the events in an individual cell to contribute to the regulation of the colony (Ben Jacob, et al., 2004). The peptide fragments that regulate bacterial colonies also influence the interactions between bacteria and more complex organisms, because stress-induced proteolysis is a universal feature of life, and very different organisms respond in similar ways to certain kinds of fragmented proteins.

The injury-induced alarm reactions that activate proteolytic enzymes in complex organisms typically release peptide fragments that are toxic to bacteria (possibly in a sort of "excitotoxicity"), and prevent their growth and invasion, while at the same time they stimulate wound healing and local cell division; if the local injury is serious enough, an amplified inflammatory reaction can involve the whole organism, its white blood cells and adaptive antibody production and hormonal and nervous reactions.

This kind of "innate immunity" is something we have in common with all forms of life. Coupled to the alarm/inflammatory system, there are more specific protective systems of regulatory peptides, that happen to be called "natriuretic peptides," although they do much more than regulating the kidneys' handling of sodium. They were first discovered in the atria of hearts, and so were called "atrial natriuretic peptide," ANP, but then peptides with similar structure and effects were found in the brain, and called "brain natriuretic peptide," BNP, and the next type to be discovered was called CNP.

Very similar peptides occur in mollusks, insects, reptiles, plants, and mammals, apparently in all multicellular organisms, and their functions in those organisms haven't been clarified, but their

universality has stimulated interest in exploring their multiple functions.

Many immunologists think of "innate immunity" as a primitive system that serves to activate the "higher" "adaptive immune system" of vertebrates. A major difference between these two systems is supposed to be the absence of memory in the innate system. In the 1950s, experimenters applied a little copper sulfate to the leaf of a plant, in a concentration just high enough to injure the tissue it touched. Then several days later, application of a highly diluted solution of the same chemical was found to cause an intense reaction and injury. The plant's "primitive" immune system demonstrated memory. "Stress memory" in plants is now more widely recognized (Goh, et al., 2003). Recent evidence (Bouché, et al., 2003; Baluška, et al., 2004; Bais, et al., 2004; Wipf, et al., 2002) supports J. C. Bose's early work showing nerve-like functions in plants.

In 1908, Ilya Mechnikov (also written Elie Metchnikoff) and Paul Ehrlich shared the Nobel prize for physiology or medicine, for their work on immunity.

Ehrlich is considered a pioneer in chemotherapy. His early work using synthetic dyes to stain bacteria and blood cells led him to the idea of a "magic bullet," in which a toxic substance (such as certain of the dyes that were being produced by the German chemical industry) would selectively kill a particular pathogen. His ideas led eventually to the current theory of using monoclonal antibodies as "magic bullets" to kill cancer cells.

Mechnikov was investigating embryology, trying to understand the principles by which an animal develops, when he realized that nutrition, especially the process of intracellular digestion of proteins, was a guiding force in the development of the organism, and later, considering the process of phagocytosis, he saw that this same principle was centrally involved in the organism's resistance to injury and infection. From seeing the place of cellular digestion and nutrition in the growth and survival of the organism, he extended his studies to the problem of the factors that influence the organism's resistance, for example why poor people are especially susceptible to infectious disease, and how toxins absorbed from the intestine weaken resistance to infections, and contribute to aging.

Acquired immunity, existing after recovering from an infection or being vaccinated, was well known to Mechnikov (he worked with Pasteur, for example), but he didn't make the extreme distinction between innate and adaptive immunity that is now often made.

For Mechnikov, the movement of cells from connective tissues into the blood, and from the blood into the endothelial and connective tissues, destroying harmful extraneous material or cells that were no longer useful, was an integral physiological process, influenced by the nervous system, to form and sustain the organism.

Although some of his contemporaries saw cellular immunity as a sort of mechanical and autonomous system (and some denounced him as a "vitalist" because of the intelligence he saw in cellular behavior), Mechnikov insisted that the processes of immunity were integral organismic processes, in which the nervous system had an essential role. Over the years, there have been many demonstrations of the brain's importance in the inflammatory process, but even the most recent studies that have found that "neuropeptides" appear to function as part of the "innate immune system" haven't achieved the comprehensive view of the organism that Mechnikov had.

Contemporary immunology and medicine see the immune system largely as Ehrlich saw it, as a specialized killing system. Like Ehrlich, few medical immunologists are interested in the similarities between plants and animals, because they see the human immune system as a unique thing evolved to more effectively destroy things which are "not-self."

The alternative view, that has grown out of Mechnikov's work, sees that the adaptiveness of plants and invertebrate animals gives us an essential perspective on our own biology. Growth, regeneration, stem cells, learning, and aging, have to be taken into account when thinking about infections, vaccinations, and the "autoimmune" diseases. We, humans and vertebrates generally, have a very intense energy metabolism that requires a powerful circulatory system that

supports a complex nervous system, but the similarities of the immune systems of the different phyla are in some ways more important than the differences. Learning or imprinting is something that can occur in any kind of cell, and the importance of the "simple" regulatory peptides of the innate immune system is now starting to be recognized in medicine.

All of our tissues, when damaged, can produce inflammation, stimulate growth, and signal to the rest of the organism that something is wrong. All, or most, of our tissues are also able to produce substances, the "natriuretic peptides," that restore stability, by reducing inflammation, inhibiting abnormal growth, increasing phagocytosis, and balancing energetic and synthetic metabolism and structural processes, including cellular differentiation, throughout the body.

The existence of these peptides in the other multicellular organisms, and the discovery that they act on pathogens (Krause, et al. 2001) as well as on the consequences of injury, suggests that they can be considered as part of the "immune system," but that recognition needn't detract from their roles in developmental, reproductive, and other basic biological processes. In the tradition of Mechnikov, it would be better to describe them as "morphostatic peptides," referring to Jamie Cunliffe's view of immunity, or "morphogenic peptides," to acknowledge that development never stops.

Cells that were once thought to cause autoimmune destruction are now known to be involved in repair and regeneration (Hofstetter, et al., 2003). Antibodies, rather than being just germ-killing proteins, or destructive autoantibodies, have many other functions, including the regulation of inflammation and regeneration (del Barco, et al., 2008; Bieber, et al., 2001; Schwartz, 2000). Phagocytes, besides eliminating foreign matter and exhausted cells, are considered to be "antigen presenting" cells that guide the adaptive immune system, but they also have an important role in guiding regeneration and differentiation of stem cells.

L.V. Polezhaev showed that processes similar to embryonic induction, guided by phagocytes, are involved in the organism's responses to damaged tissues. For example, when a piece of killed muscle tissue was enclosed in a porous capsule that permits molecules, but no cells, to diffuse through it, and implanted subcutaneously, it had no inductive effect on surrounding cells. But when the pores of the capsule allowed cells to enter, skeletal muscle formed where the dead tissue had been, and tissue resembling heart muscle formed outside the capsule. Phagocytosis had been essential for the induction to occur. The ingested material guided the differentiation of the surrounding cells.

The phagocytosis function isn't limited to the blood cells commonly called phagocytes; even nerve cells can ingest particles and fragments of damaged tissues. Polezhaev believed that fats were an inmportant factor in stimulating regeneration, and recent research shows that saturated fats and unsaturated fats have very different effects on the antigen presenting cells (Shaikh, et al., 2008). The innate immune system is probably impaired as a result of the cumulative toxicity of the polyunsaturated fats, contributing to the problems of aging.

Unsaturated fatty acids inhibit phagocytosis (Guimaraes, et al., 1991, 1992; Costa Rosa, et al., 1996; Virella, et al., 1989; Akamatsu, et al., 1990), and accumulate with aging. Phagocytosis decreases with aging, while other immune functions may increase. The age pigment, lipofuscin, consisting largely of oxidized polyunsaturated fats, impairs the phagocytic function even before it becomes grossly visible. The highly oxidizable n-3 polyunsaturated fats (Virella, et al., 1989) appear to be the most harmful to immunity against infections such as tuberculosis (Paul, et al., 1997).

ANP activates the phagocytic processes, while inhibiting inflammation (Borán, et al. 2008; Vollmar, et al., 1997).

The use of one of these nontoxic natriuretic peptides (BNP) as a drug for treating heart failure has possibly been helpful (Mohammed, et al., 2008), and now others have been discovered to be very active against cancer (Vesely, et al., 2006, 2008), but it shouldn't be necessary to wait for their availability as drugs, since their secretion can be induced by ordinary physiological means. Mechnikov and his contemporaries concentrated

mainly on trying to reduce the absorption of bacterial toxins from the intestine to preserve or restore the basic defensive and restorative processes, but in the last century new approaches have become possible.

Since these peptides were called "natriuretic" because of their effects on salt and water regulation, it seems reasonable to consider them in situations in which there are problems with the regulation of water and salt. Premenstrual syndrome, preeclampsia or pregnancy hypertension, congestive heart failure, brain swelling and seizures all involve disturbances of salt and water regulation, but the mechanical medical tradition has almost always substituted beliefs for facts.

Because of beliefs about cell physiology, most medical publications have argued for sodium restriction in those situations, but the evidence is clear that **inadequate salt retention** is usually their outstanding pathological feature.

Progesterone has been an effective treatment in all of those conditions, and it increases the ability of the kidneys to retain sodium. Progesterone increases ANP, and together they prevent sodium loss. (Because of this, it would be better to think of ANP as an *anti*natriuretic, rather than a natriuretic, peptide.) Each of them helps to prevent excessive vascular permeability (leakiness), and to inhibit the secretion of the antidiuretic hormone (ADH, or vasopressin) from the pituitary. ADH causes sodium loss, water retention, vascular leakiness, and constriction of arterioles, increasing blood pressure while decreasing the delivery of oxygen to the tissues, and increasing the tendency of blood to clot inappropriately.

Drugs to antagonize ADH are available, and are sometimes used to treat heart failure; these drugs help to **increase** sodium retention. Aldosterone antagonists (synthetic variations of progesterone) are also used to treat heart failure; they cause sodium to **decrease.** Progesterone, and the ANP it stimulates, would inhibit both ADH and aldosterone, regulating sodium and blood pressure and improving kidney function, while (like digitalis) progesterone strengthens the heart's contraction. The reason progesterone isn't used seems to be that no drug company promotes its use.

Estrogen is often recommended to "protect the heart," and even to treat heart failure, but it lowers ANP, increases ADH/vasopressin, causes water retention and sodium loss, vascular leakiness, and (like aldosterone) weakens the heart's contraction. Part of estrogen's action on capillaries results from increasing the vascular permeability factor (VPF), which is now called vascular endothelial growth factor (VEGF). This growth factor contributes to degenerative problems including diabetes, glaucoma, arthritis, atherosclerosis, and cancer, and blocking it can cause cancers to regress. ANP blocks the production and vascular action of VEGF (Pedram, et al., 2006). Both ANP and BNP protect against excessive permeability (Klinger, et al., 2006).

Thyroid hormone, like progesterone, also increases ANP, and, probably acting through increased carbon dioxide, is essential for regulating sodium and water. Hypertonic sodium chloride and increased carbon dioxide, in themselves, increase the formation of ANP. Caffeine is another substance which inhibits VEGF, while increasing ANP.

When an imbalance of these hormones allows too much sodium to be lost, and too much water to be retained, the phagocytic cells swell, and their autophagic and phagocytic activity is impaired, making the organism more susceptible to infection. Simply correcting the osmotic balance by supplementing salt can improve immune function (Junger, et al., 1994), as it stimulates respiratory metabolism, and increases carbon dioxide and body temperature. Increased carbon dioxide promotes tissue remodeling, lowers stress, and increases the synthesis of ANP (Kukacka, et al., 2007).

ANP protects against stress-induced excitatory effects of calcium (Green, et al., 2007; *Kuribayashi*, et al., 2006; Tian and Yang, 2006; Yoshioka, et al., 2000; Wang, et al., 1993).

Intracellular calcium overload is an essential feature of heart failure and hypertrophy (Malyshev Ilu, Meerson, 1990). Both vitamin D and vitamin K require carbon dioxide for disposing of calcium properly, preventing its toxicity. When carbon dioxide is inadequate, for example from simple hyperventilation or from hypothyroidism, calcium

is allowed to enter cells, causing inappropriate excitation, sometimes followed by calcification.

Keeping an optimal level of carbon dioxide (for example, when adapted to high altitude) causes calcium to be controlled (Arkhipenko, et al., 1992), resulting in lowered parathyroid hormone (PTH), an effect similar to supplementing with calcium, vitamin D, and vitamin K. (E.g., Nicolaidou, et al, 2006.) The contribution of PTH to inflammation and degeneration is just being acknowledged (e.g., Kuwabara, 2008). It suppresses phagocytosis (Esposito, et al., 1988; Smogorzewski, et al., 2001), probably by causing calcium overload, but in other situations it stimulates proliferation of lymphocytes and T cells (Klinger, et al., 1990; Adachi, et al., 1990).

The thyroid hormone, producing carbon dioxide, helps to sustain the level of ionized calcium (Lindblom, et al., 2001). In a vitamin D deficiency, or a calcium deficiency, the parathyroid hormone increases, and this hormone can contribute to many inflammatory and degenerative processes, including heart failure (Smogorzewski, 1995; Halapas, et al., 2006; Sugimoto, et al., 2008) and cardiac hypertrophy (Liu, et al., 2008). ANP and PTH have opposite effects on cellular calcium handling, and increasing the oral intake of calcium increases ANP (Halabe, et al., 1990), but lowers PTH.

Consuming enough calcium and vitamin D to keep the parathyroid hormone suppressed (and to support ANP) is important to protect against the degenerative conditions.

In organisms with a lower rate of metabolism, the regulatory substances are more closely associated with the organisms' structure, but in homeothermic animals with a high rate of metabolism, nerves and circulating hormones serve to reinforce the basic processes of immunity, allowing the whole organism to adapt coherently to sudden changes in its situation. These hormonal and nervous systems have "polarities" that are analogous to those of the innate peptide system, i.e., one side to defend and alarm and promote growth, another side to restore coherence and functions. The defensins are balanced by the "natriuretic peptides," while estrogen, VEGF, and ADH are balanced by progesterone and thyroid, and by the osmolarity, carbon dioxide, and heat that they sustain. The antimicrobials accelerate healing, but they also stimulate tumor growth, when they aren't balanced by the opposing systems.

Mechnikov was right in seeing bacterial toxins from the intestine as a cause of aging, and he was on the right track in trying to introduce a more beneficial bacterial ecology into the intestine by using sour milk. The lactobacilli do have some protective effects, but the lactic acid that they produce turns out to function as an alarm signal, which accelerates the same aging processes that the other bacterial endotoxins produce.

When these simple physical and chemical factors are well balanced, metabolism renews the structure of the organism, directing the differentiation of new cells and adjusting the composition of the intercellular substance, according to the type of stress the organism is experiencing.

Mechnikov's emphasis on the developmental, formative nature of the immune system, combining embryology and nutritional physiology with immunity, created the foundation for the understanding of regeneration and stem cell functions. Wandering cells can become structural parts of the fixed tissues and organs (Rohde, et al., 2007), or they can remove debris and call for more phagocytic cells, or they can signal for replacement stem cells and guide their differentiation.

Local-systemic interactions, in which local events cause systemic changes, and systemic events cause local changes, have been neglected and misinterpreted, especially where the "immune system" is concerned.

The recent renewal of interest in inflammation as a basic cause of chronic and degenerative disease, is a first step toward an integral therapeutic system, even though the systemic restorative processes are still being neglected.

Bacterial endotoxins are probably the central problem, but polyunsaturated fats, heavy metals, and extraneous hormones interact with them, extending their toxic actions.

Reducing the toxic factors, relative to the restorative factors, should be the aim, rather than looking for another drug.

When even a natural, endogenous substance is used as "a drug," the way it is conceptualized and

named is likely to reinforce the mechanical models of the organism, and those models are always inadequate. If we see health problems as events in an organism's adaptation to a problematic environment, the focus is shifted to the defects in the environment that might be remedied.

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Ray Peat's Newsletter

Many a small thing has been made large by the right kind of advertising. Mark Twain

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Resveratrol, rate of living, CO2, and aging

A year ago GlaxoSmithKline bought Sirtris, a company focusing on the biological effects of resveratrol, for $720,000,000. Harvard Medical School's website, and broadcasts by Barbara Walters and Morley Safer have publicized resveratrol as a longevity-increasing drug, and millions of people are spending large amounts of money for resveratrol capsules.

The main claim being made about resveratrol is that it can mimic the anti-aging effects of calorie restriction, without having to restrict food consumption. This involves silencing genes, blocking their production of RNA and protein.

The mass media and some medical journals aren't giving a balanced description of the biological effects of resveratrol, but many biologists are being influenced too, by the same simple arguments that the television reporters summarized. The academic biology culture, the medical culture, and the basic American culture itself, are all permeated by the idea of genetic determinism, so when a DNA molecule in yeast is identified as the "anti-aging gene," and a molecule is found that activates it, that molecule, or something similar, seems to them clearly to be an anti-aging drug.

Part of the cultural framework that makes it easy to sell that idea is the old "rate of living" theory of aging, the idea that we have only so many heartbeats in a lifetime, that we can use only so many calories and so much oxygen in a lifetime, and that organisms with a low metabolic rate therefore live longer than those with a high metabolic rate. The rate of living theory is closely related to the "wear and tear" theory of aging, that our bodies are (except for our germ cells) made up of "post-mitotic cells," unable to continue dividing once growth is complete, and so must die when those cells are "worn out." By the middle of the 20th century, those ideas had been disproved in many ways, but in the 1960s Leonard Hayflick renewed for a time the doctrine of aging as the wearing out of unrenewable cells, with his doctrine that somatic cells (non-germ cells) have an absolute limit of 50 replications. Producing cloned animals from somatic cells, and the subsequent excitement about stem cells, made that theory obsolete (again).

The "longevity gene," named Sir2 in yeasts, worms, and flies (its equivalent in mammals is called SirT1), is activated by restricting calories, and caloric restriction is known to extend lifespan (though the restriction of certain nutrients can similarly increase longevity, without restricting calories). Both semi-starvation and increased activity of the Sir2 gene can prevent obesity, and obesity has some harmful effects. The promoters of the theory suggest that a resveratrol-like drug will be able to prevent obesity and cure type-2 diabetes. They are also suggesting that it could slow aging and increase longevity.

Talking about the "aging" of a single-celled organism such as yeast, and drawing conclusions about the aging of multicellular organisms and humans, from events in the life of yeast, is meaningful only to people who subscribe to the Hayflick doctrine, and who deny the reality of stem cells in mammals and other complex organisms. They are actually talking about the "fertility," the reproductive growth capacity, of the yeasts. The study of yeast metabolism and growth developed mostly in relation to the needs of the wine and beer industries, and that has biased ideas about the ways yeast adapts to changing ecosystems. Yeasts adapt their reproductive strategy to the perceived adequacy of their environment. An individual yeast cell coordinates its physiology with the surrounding cells, in ways

analogous to the ways individual cells in an animal participate in the coherence of the organism.

As in higher organisms, stress can accelerate the reproductive process in yeast. In animals, stress can cause precocious puberty, as if they were being exposed to an excess of estrogen. Resveratrol is a defensive fungicidal antibiotic, or phytoalexin, so it's reasonable that it would be perceived as a stressor by yeast. It is also a phytoestrogen, and for many years yeasts have been known to be responsive to estrogenic substances. To the brewing industry, these effects of phytoestrogens are known to influence the biomass, but when the rate of growth is considered to represent aging, then increased biomass is equivalent to increased longevity.

Anyone familiar with the last 40 years of yeast research would presumably know that phenolic phytoalexins are estrogenic, and that the growth of yeast is influenced by estrogenic substances, and also that estrogenic substances such as resveratrol could be very dangerous if consumed in exaggeratedly large amounts.

Resveratrol is a stilbene, similar in structure to diethylstilbestrol, DES, the famously toxic-carcinogenic pharmaceutical. Estrogens affect all of the systems affected by resveratrol, and for 67 years, the estrogen industry has been telling the public that whatever estrogen does is beneficial---more than 200 medical conditions have been benefited by estrogen treatment, according to the medical literature/pharmaceutical advertising.

Many people have been asserting that the reason calorie restriction can extend life is that it activates "the antiaging gene, Sir2." A recent publication (Carrano, et al., 2009) from the Salk institute proposes that two other genes are responsible for calorie-restriction longevity in the roundworm, C. elegans.

But restricting calories has a multitude of effects--Sir2 is only one of hundreds of genes that function differently in hunger-stressed animals. Calorie restriction is stressful, but the nature of that stress and the response to it depends on the whole situation, just as in any other challenging situation.

One problem with the Sirtris scheme is that increased Sir2 activity shortens the actual chronological lifespan of non-dividing yeast (Kennedy, et al., 2005; Fabrizio, et al., 2005). In animals, increasing the activity of SirT1 might contribute to the development of cancer (Liu, et al., 2009). It might also be involved in Alzheimer's disease, and the replacement of nerve cells in the brain with astrocytes or other glial cells. Gliosis can occur in normal aging, but inflammation can produce extreme degrees of fibrosis of the brain or spongy encephalopathy. Estrogens also have this effect of accelerating stem cell production of glial cells.

In a recent study, to determine whether resveratrol would slow the heart rate and lower the body temperature in mice (as expected according to the rate of aging doctrine), those metabolic indicators were depressed by resveratrol for one day, but then returned to normal. However, the endurance of the mice on a treadmill was reduced by the resveratrol treatment (Mayers, et al., 2009).

Going beyond the Sir2 gene-based argument, many researchers have examined resveratrol's effects on various other genes. Too often, it seems that the authors reason that whatever resveratrol does to those genes must be good for the organism. These arguments seem to be following the reasoning that has been systematically used to promote estrogen and polyunsaturated fats.

If we consider the effects of resveratrol in the context of the well established facts about the metabolic processes associated with long life, we will notice many things that should lead to skepticism about the claims being made by the advertisers.

A little stress can make an organism more resistant to subsequent stresses. However, resveratrol fails to extend the lifespan of normal mice, being effective only in a strain of mice that becomes abnormally fat on a normal diet.

About 40 years ago, when people first began promoting fish oil as a longevity factor, Alex Comfort watched the rats that were being given the fish oil in their food. The food smelled bad, and the rats ate it only when they were very hungry, so they ate less and were leaner than the animals that were getting the standard diet. Their increased longevity was the result of avoiding obesity.

In a long-term study at NIH, rhesus monkeys are being studied to learn whether calorie restriction extends the lifespan of primates, as it does certain (genetically fat) rodents. The monkeys are kept in small cages. Confinement causes severe stress. Rats that are allowed to bite something while restrained suffer less physical stress, fewer ulcers, and are more able to maintain normal body temperature. Restraint normally lowers body temperature, lowering thyroid and increasing cortisol.

Eating in response to stress ameliorates some of the hormonal changes, but the monkeys that are permitted to eat as much as they want during their life of confinement have become very obese. They look much less agitated than the low calorie monkeys, and their body temperatures are higher.

The rate-of-living doctrine causes the researchers to reason that the low-calorie diet is slowing the rate of aging by lowering their body temperature. However, their metabolic rate, per gram of non-fat tissue, hasn't decreased.

An important difference that has been observed is that the chromosomes of the calorie deprived monkeys have more defects.

Nitric oxide, which is promoted by resveratrol, according to numerous publications (Klinge, et al., 2008; Gresele, et al. 2008; Gan, et al., 2009), and estrogens (acting partly through nitric oxide), including some phytoestrogens, cause chromosomal damage (Banerjee, et al., 1994; Kulling, et al., 1999) which contributes to cancer and possibly to birth defects. Nitric oxide has been proposed to be a major factor in causing the degenerative diseases of aging.

If these monkey experiments have any relevance to human biology, it is to demonstrate that prolonged torture by confinement and food restriction causes bodily damage, in the form of chromosomal abnormalities. But unless the next generation of monkeys is examined for birth defects and other problems, the full meaning of the experiment won't be apparent.

In some of the publications claiming that resveratrol increases lifespan, it was reported that niacinamide had the opposite effect, suppressing Sir2, the longevity gene, and shortening the organism's lifespan. To put their claims into context, it's helpful to look at a variety of experiments involving treatment with niacinamide.

It protects nerves, vascular cells, insulin-producing cells in the pancreas, and a variety of other types of cell from cell death produced by lack of oxygen, excitotoxicity, endotoxin, and a variety of stressors and toxins. (Niacinamide acts in many ways as a negation of resveratrol; for example, resveratrol interferes with the ability of the beta cells to secrete insulin [Szkudelski, 2007]).

Niacinamide protects mitochondrial respiration from many of the age-related factors that can damage mitochondria and decrease energy production. Lipopolysaccharide, the bacterial endotoxin, increases the production of the free radical nitric oxide, leading to the secretion of inflammatory mediators and the suppression of energy production by the mitochondria. These effects are blocked by niacinamide (Fukuzawa, et al., 1997). Calorie restriction also protects mitochondrial respiration, in yeasts (Lin, et al., 2002) and rats (Broderick, et al., 2002)

The "replicative lifespan" of human cells in vitro is extended by treatment with niacinamide (Kang, et al., 2006).

In an experiment with human keratinocytes *in vitro,* resveratrol had the opposite effect, reducing their ability to divide (Blander, et al., 2009). By the definitions of "aging" used by the advocates of the rate-of-living theory, this experiment suggests that resveratrol causes premature aging. Estrogen has a similar effect on keratinocytes. Resveratrol, nitric oxide, and estrogen, unlike niacinamide, suppress mitochondrial respiration. Resveratrol inhibits the formation of progesterone (Chen, et al., 2007), which is synthesized in mitochondria.

The NIH researchers reported that the food deprived monkeys (contrary to their expectation) didn't have a lower rate of metabolism, but many experiments done with a variety of very different animals through much of the last century found that a ***higher*** metabolic rate corresponded to increased longevity. Within a given species of bird or mammal, the higher rate of metabolism is often associated with a higher body temperature, and a long life span.

But when different types of animal of very different sizes are compared, smaller animals may have a higher rate of metabolism, but a shorter lifespan, than a larger animal, as in the case of mice and elephants. This example was used recently by an endocrinologist, Martin Surks, to argue against treating "subclinical hypothyroidism." He suggests that hypothyroid people, who have a lower rate of metabolism than euthyroid people, are likely to live longer, because their metabolism is analogous to the slow metabolism of elephants, rather than the fast metabolism of mice.

Comparing animals of different species, such as birds, monkeys, and rodents, of similar sizes, those with the highest metabolic rate are likely to have the longest average and maximum lifespans.

The smaller an organism is, the more easily it loses heat to the environment. Most of a mouse's metabolic energy is spent simply maintaining its body temperature. Large animals have less surface area in proportion to their mass, so they spend relatively little energy in temperature regulation.

One of the ideas deeply associated with the rate-of-living theory of aging is that our metabolic energy is spent mainly for regulating the concentration of salts and other substances in cells, with a small amount used for secretion, movement, and--a relatively recent admission--for thought.

Gilbert Ling has demonstrated the falsity of the idea that "membrane pumps" regulate the concentratons of dissolved materials, and showed that the amount of energy needed to operate them constantly would be much greater than the metabolic capacity of any organism.

The fact that those "membrane-based" energy consuming processes don't exist leaves a lot of energy to be accounted for. One of the main energy-consuming activities of a cell is just being alive, that is, adapting, sensing, responding, anticipating, orienting itself to its environment. Except in very special circumstances, the substance of a cell is in constant motion, and the molecules are being consumed and reconstructed, in a process of continuous renewal. These intracellular streams of renewal of molecules and organelles are paralleled on the scale of tissues and organs by a process of renewal, in which new cells are born and unnecessary cells are dissolved.

Part of the "rate of living" relates to the rate of renewal of the organism. Another part relates to issues such as the loss of heat, that makes life shorter and harder for very small animals.

The end product of respiration is carbon dioxide, and it is an essential component of the life process. The ability to produce and retain enough carbon dioxide is as important for longevity as the ability to conserve enough heat to allow chemical reactions to occur as needed.

Carbon dioxide protects cells in many ways. By bonding to amino groups, it can inhibit the glycation of proteins during oxidative stress, and it can limit the formation of free radicals in the blood; inhibition of xanthine oxidase is one mechanism (Shibata, et al., 1998). It can reduce inflammation caused by endotoxin/LPS, by lowering the formation of tumor necrosis factor, IL-8 and other promoters of inflammation (Shimotakahara, et al., 2008). It protects mitochondria (Lavani, et al., 2007), maintaining (or even increasing) their ability to respire during stress.

The "replicative lifespan" of a cell can be shortened by factors like resveratrol or estrogen that interfere with mitochondrial production of carbon dioxide. Both of those chemicals cause skin cells, keratinocytes, to stop dividing, to take up calcium, and to begin producing the horny material keratin, that allows superficial skin cells to form an effective barrier. This process normally occurs as these cells differentiate from the basal (stem) cells and, by multiplying, move farther outward away from the underlying blood vessels that provide the nutrients that are oxidized to form carbon dioxide, and as they get farther from the blood supply, they get closer to the external air, which contains less than 1% as much CO2 as the blood. This normally causes their eventual hardening into the keratin cells, but when conditions are optimal, numerous layers of moist, translucent cells that give the skin the characteristic appearance of youth, will be retained between the basal cells and the condensed surface layers. (Wilke, et al., 1988)

In other types of tissue, a high level of carbon dioxide has a similar stabilizing effect on cells, preserving stem cells, limiting stress and preventing loss of function. In the lining of the mouth, where the oxygen tension is lower, and carbon

dioxide higher, the cells don't form as much keratin as the skin cells do. In the uterus, the lining cells would behave similarly, except that estrogen stimulates keratinization. A vitamin A deficiency mimics an estrogen excess, and can cause excessive keratinization of membrane cells.

Yeasts adapt their physiology and life cycle to their particular ecological situation. The cells within an animal behave analogously, but that is likely to be forgotten or denied, because of the culture of genetic determinism.

The cells in each organ and tissue of the body are arranged in ways that allow them to make their contribution to the function of the organism, while receiving oxygen, glucose, and regulatory substances in the blood, and maintaining and renewing themselves. Except for the skin, their situation amid other cells assures that they will live in a high concentration of carbon dioxide.

There are proteins (uncoupling proteins, UCP) that cause the mitochondria to increase their consumption of oxygen without increasing their synthesis of ATP. The synthesis of ATP is usually thought of as the main reason for the consumption of oxygen, so the UCP have been assumed to exist to increase heat production. The formation of carbon dioxide is usually thought of as just an unavoidable consequence. UCP proteins, however, exist in situations in which heat production doesn't seem appropriate (Borecký & Vercesi, 2005; Aguilera, et al., 2005; Gnanalingham, et al., 2005). For example, fasting or calorie restriction increases UCP, tending to cause tissues to consume energy more rapidly. Stress and hypoxia also can increase UCP, suggesting that these enzymes have protective functions.

Increasing the formation of carbon dioxide seems to me to be the essential function of the UCP. Thyroid hormone (T3) increases UCP, and UCP increases the formation of new mitochondria. Increased activity of the UCP is closely associated with increased lifespan. A decreased amount of T3 in tissues during aging corresponds to decreasing mitochondrial functon.

Increased CO2 inhibits the formation of lactate, decreases the lipolytic effect of adrenaline, and the lowered energy charge produced by the UCP would prevent the diversion of glucose into other uses.

According to the rate-of-living theory of aging, the "post-mitotic" organism ages and degenerates in proportion to the rate at which it metabolizes. Leonard Hayflick, to demonstrate that it is cell division, not the passage of time, that ages cells, put some cells in a freezer, while others, from the same batch, were kept in a warm incubator and allowed to go through their allotted number of divisions. When the warm, growing cells had approached 50 replications and began dying "of old age," the other cells were taken out of the freezer, and they were able to divide as well as they had before being frozen. The implication was that slowing metabolism was the only way to extend the lifespan.

These beliefs have allowed people to view the metabolism, the turnover of substance and cells, of a tissue such as bone, as indicating breakdown, weakening, and loss. For many years, it was impossible to show any beneficial effect of estrogen on the bones of experimental animals or people, but then it was discovered that it could slow the metabolism of the osteoclasts, reducing the rate of turnover in the bones. This was propagandistically effective.

The estrogen industry's funding greatly reinforced the rate-of-living theory of aging, and metabolic markers of bone turnover began to be used to measure the effects of treatment. Thyroid hormone (the active T3 hormone) increases the rate of turnover of all tissues, including bone, so by reference to the "bone protective effects of estrogen," the argument was made that thyroid supplementation should be reduced, to prevent osteoporosis (despite animal studies showing that T3 increases bone development). Since hypothyroidism usually involves increased thyroid stimulating hormone, TSH, the argument was extended by showing that TSH lowers bone turnover.

One factor involved in the increased production of TSH in hypothyroidism is that the low metabolic rate allows estrogen to accumulate, leading to increased serotonin production. Serotonin stimulates both TSH and prolactin. Serotonin and prolactin both happen to cause bone loss. They increase nitric oxide, which inhibits mitochondrial respiration. Serotonin increases a cytokine, osteoprotegerin, that inhibits osteoclasts, reducing bone turnover. However,

serotonin's other antimetabolic effects outweigh that effect, and it is a major factor in causing osteoporosis. The antimetabolic factors that slow the rate of living also slow the rate of renewal, and on balance lead to tissue atrophy, fibrosis, inflammation, and degeneration. Several decades after estrogen-induced prolactin might have been recognized as a cause of bone loss in aging, a few people are mentioning the mechanism in specific situations (Horner, 2009; Horner, et al., 2007).

With aging, metabolic activity and the turnover of biological substance decrease. Organelles such as mitochondria are renewed every day or two, much of the brain substance has a similarly fast rate of turnover, and other parts of the body are renewed more slowly. When conditions are optimal, the new structures are flawless, but under the wrong conditions, faulty repairs can accumulate, producing the degenerative problems of aging.

Our culture's understanding of biology has been shaped by a series of ideologies, and currently the drug industry is the main force shaping those ideologies, creating an attitude that's receptive to their products.

The huge marketing campaign for resveratrol will have direct effects on people's health, probably extending beyond the generation that uses it, but it is also polluting the culture by reinforcing the doctrine that torpor, slowing the life process, is beneficial.

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Ray Peat's Newsletter

"The cell is always speaking--the secret is to learn its language." --Andrew S. Bajer

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Glucose and sucrose for diabetes

Diabetes has been known since ancient times as a wasting disease in which sugar was lost in the urine, but more recently the name has been used to describe the presence of more than the normal amount of glucose in the blood, even in the absence of glucose in the urine. Some of the medical ideas regarding the original form of the condition have been applied to the newer form.

Cultural "paradigms" or ideologies are so convenient that people often don't bother to doubt them, and they are sometimes so rigorously enforced that people learn to keep their doubts to themselves. Public concern about diabetes has been growing for decades, but despite the introduction of insulin and other drugs to treat it, and massive campaigns to "improve" eating habits, mortality from diabetes has been increasing during the last 100 years. Diabetes ("type 1") has been increasing even among children (Barat, et al., 2008).

A basic meaning of homeopathic medicine is the support of the organism's ability to heal itself; the essence of allopathy is that the physician fights "a disease" to cure the patient, e.g., by cutting out tumors or killing germs.

Confidence in the organism's essential rationality led the doctors with a homeopathic orientation to see a fever as part of a recuperative process, while their allopathic opponents sometimes saw fever as the essence of the sickness to be cured. Homeopaths concentrated on the nature of the patient; allopaths concentrated on a disease entity in itself, and were likely to ignore the patient's idiosyncrasies and preferences.

Diabetes was named for the excessive urination it causes, and for the sugar in the urine. It was called the sugar disease, and physicians were taught that sugar was the problem. Patients were ordered to avoid sweet foods, and in hospitals they were sometimes locked up to keep them from finding sweets. The practice was derived from ideology, not from any evidence that the treatment helped.

In 1857, M. Piorry in Paris and William Budd in Bristol, England, reasoned that if a patient was losing a pound of sugar every day in 10 liters of urine, and was losing weight very rapidly, and had an intense craving for sugar, it would be reasonable to replace some of the lost sugar, simply because the quick weight loss of diabetes invariably led to death. Keeping patients from eating what they craved seemed both cruel and futile.

After Budd's detailed reports of a woman's progressive recovery over a period of several weeks when he prescribed 8 ounces of sugar every day, along with a normal diet including beef and beef broth, a London physician, Thomas Williams, wrote sarcastically about Budd's metaphysical ideas, and reported his own trial of a diet that he described as similar to Budd's. But after two or three days he decided his patients were getting worse, and stopped the experiment.

Williams' publication was presented as a scientific refutation of Budd's deluded homeopathic ideas, but Budd hadn't explained his experiment as anything more than an attempt to slow the patient's death from wasting which was sure to be the result of losing so much sugar in the urine. The following year Budd described another patient, a young man who had become too weak to work and who was losing weight at an extreme rate. Budd's prescription included 8 ounces of white sugar and 4 ounces of honey every day, and again, instead of increasing the amount of glucose in the urine, the amount decreased quickly as the patient began eating almost as much sugar as was

being lost initially, and then as the loss of sugar in the urine decreased, the patient gained weight and recovered his strength.

Drs. Budd and Piorry described patients recovering from an incurable disease, and that has usually been enough to make the medical profession antagonistic. Even when a physician has himself diagnosed diabetes and told a patient that it would be necessary to inject insulin for the rest of his life, if that patient recovers by changing his diet, the physician will typically say that the diagnosis was wrong, because diabetes is incurable.

Twenty-five years ago, some rabbits were made diabetic with a poison that killed their insulin-secreting pancreatic beta-cells, and when some of them recovered from the diabetes after being given supplemental DHEA, it was found that their beta-cells had regenerated. The more recent interest in stem cells has led several research groups to acknowledge that in animals the insulin-producing cells are able to regenerate.

It is now conceivable that there will be an effort to understand the factors that damage the beta-cells, and the factors that allow them to regenerate. The observations of Budd and Piorry would be a good place to start such a reconsideration.

For many years, physicians have been taught that diabetes is either "genetic" or possibly caused by a viral infection, that might trigger an "autoimmune reaction," but the study of cellular respiration and energy metabolism and endocrinology has provided more convincing explanations. The antibodies that are found in the "autoimmune" conditions are evidence of tissue damage, but the damage may have been done by metabolic toxins, with the immune system's involvement being primarily the removal of defective cells.

In the 1940s, Bernardo Houssay found that coconut oil protected animals from poison-induced diabetes, while a lard-based diet failed to protect them. Later, glucose itself was found to protect the pancreatic beta-cells from poisons.

In 1963, P.J. Randle clearly described the inhibition of glucose oxidation by free fatty acids. Later, when lipid emulsions came into use for intravenous feeding in hospitals, it was found that they blocked glucose oxidation, lowered the metabolic rate, suppressed immunity, and increased lipid peroxidation and oxidative stress.

Estrogen and stress are both known to create some of the conditions of diabetes, while increasing fat oxidation and inhibiting glucose oxidation. Emotional stress, overwork, trauma, and infections have been known to initiate diabetes. Estrogen increases free fatty acids and decreases glycogen storage, and when birth control pills were becoming popular, some researchers warned that they might cause diabetes. But the food oil industry and the estrogen industry were satisfied with the medical doctrine that diabetes was caused by eating too much sugar.

If the essence of diabetes is the presence of too much sugar, then it seems reasonable to argue that it is the excess sugar that's responsible for the suffering and death associated with the disease, otherwise, how would the prohibition of sugar in the diet be justified? In fact, the argument is made (e.g., Muggeo, 1998) that it is the hyperglycemia that causes problems such as hypertension, kidney failure, heart failure, neuropathy, blindness, dementia, and gangrene.

As information about the many physiological and biochemical events associated with diabetes has accumulated, the basic doctrine that "sugar causes diabetes" has extended itself to whatever the topic of discussion is: "Glucose causes" the death of beta-cells, glucose causes blood vessels to become leaky, glucose causes cells to be unable to absorb glucose, glucose causes the formation of free radicals, glucose impairs immunity and wound healing, but causes inflammation while preventing the "respiratory burst" in which free radicals are produced by cells that cause inflammation, it disturbs enzyme functions, impairs nerve conduction and muscle strength, etc., and it is also addictive, causing people to irrationally seek the very material that is poisoning them.

Tens of thousands of publications describe the pathogenic effects of sugar. To prove their point, they grow cells in a culture dish, and find that when they are exposed to excess glucose, often 5 times the normal amount, they deteriorate. In the artificial conditions of cell culture, the oversupply of glucose causes lactic acid to accumulate,

leading to toxic effects. But in the organism, the hyperglycemia is compensating for a sensed deficiency of glucose, a need for more energy.

If diabetes means that cells can't absorb or metabolize glucose, then any cellular function that requires glucose will be impaired, despite the presence of glucose in the blood. It is the intracellular absence of glucose which is problematic, rather than its extracellular excess.

Neuroglycopenia (or neuroglucopenia) or intracellular glycopenia refers to the deficit of glucose in cells. When the brain senses a lack of glucose, nerves are activated to increase the amount of glucose in the blood, to correct the problem. As long as the brain senses the need for more glucose, the regulatory systems will make the adjustments to the blood glucose level.

The antagonism between fat and sugar that Randle described can involve the suppression of sugar oxidation when the concentration of fats in the bloodstream is increased by eating fatty food, or by releasing fats from the tissues by lipolysis, but it can also involve the suppression of fat oxidation by inhibiting the release of fatty acids from the tissues, when a sufficient amount of sugar is eaten.

When a normal person, or even a "type 2 diabetic," is given a large dose of sugar, there is a suppression of lipolysis, and the concentration of free fatty acids in the bloodstream decreases, though the suppression is weaker in the diabetic (Soriguer, et al., 2008). Insulin, released by the sugar, inhibits lipolysis, reducing the supply of fats to the respiring cells.

Free fatty acids suppress mitochondrial respiration (Kamikawa and Yamazaki, 1981), leading to increased glycolysis (producing lactic acid) to maintain cellular energy. The suppression of mitochondrial respiration increases the production of toxic free radicals, and the decreased carbon dioxide makes the proteins more susceptible to attack by free radicals. The lactate produced under the influence of excessive fat metabolism stimulates the release of endorphins, which are lipolytic, releasing more free fatty acids from the tissues. Acting through cytokines such as interleukin-6, lactate shifts the balance toward the catabolic hormones, leading to tissue wasting.

Lactic acid itself, and the longer chain fatty acids, inhibit the regulatory enzyme pyruvate dehydrogenase (which is activated by insulin), reducing the oxidative production of energy. Drugs to activate this enzyme are being studied by the pharmaceutical industry as treatments for diabetes and cancer (for example, DCA, dichloroacetate).

Oxidative damage of proteins is often described as glycation or glycosylation, but it really consists of many addition and crosslinking reactions, most often onto, or between, lysine groups. Carbon dioxide normally associates with lysine groups, so the destructive reactions are favored when carbon dioxide is displaced by lactic acid. The reactive fragments of polyunsaturated fatty acids are much more often the source of the protein-damaging radicals than the carbohydrates are.

The importance of the fats in causing type-2 diabetes is coming to be accepted, for example Li, et al., recently (2008) said "The cellular link between fatty acids and ROS (reactive oxygen species) is essentially the mitochondrion, a key organelle for the control of insulin secretion. Mitochondria are the main source of ROS and are also the primary target of oxidative attacks."

But much earlier (Wright, et al., 1988) it had been demonstrated that a deficiency of the "essential fatty acids" prevents toxin-induced diabetes and greatly increases resistance to inflammation (Lefkowith, et al., 1990). The lack of those so-called "essential fatty acids" also prevents autoimmune diabetes in a strain of diabetic mice (Benhamou, et al., 1995),

Suppressing fatty acid oxidation improves the contraction of the heart muscle and increases the efficiency of oxygen use (Chandler, et al., 2003). Various drugs are being considered for that purpose, but niacinamide is already being used to improve heart function, since it lowers the concentration of free fatty acids.

The antimetabolic and toxic effects of the polyunsaturated fatty acids can account for the "insulin resistance" that characterizes type-2 diabetes, but similar actions in the pancreatic beta-cells can impair or kill those cells, creating a deficiency of insulin, resembling type-1 diabetes.

The suppression of mitochondrial respiration causes increased free radical damage, and the presence of polyunsaturated fatty acids in the suppressed cell increases the rate of fat decomposition and production of toxins.

Increasing the rate of respiration by replacing the fats with glucose reduces the availability of electrons that can trigger lipid peroxidation and produce toxic free radicals, and the shift of fuel also increases the amount of carbon dioxide produced, which can protect the protein amino groups such as lysine from glycation and lipoxidation.

While it's clear that it is the excessive oxidation of fat that damages cells in the "diabetic" state in which cells aren't able to use glucose, it's important to look at some of the situations in which so many researchers are blaming problems on hyperglycemia.

Important problems in diabetes are slow wound healing, excessive permeability or leakiness of blood vessels which allows molecules such as albumin to be extravasated, and the impaired function and survival of pancreatic beta-cells.

During the healing of a wound in a diabetic individual, the local concentration of glucose decreases and then entirely disappears, as healing stops. Applying glucose and insulin topically to the wound, it heals quickly. The very old practice of treating deep wounds with honey or granulated sugar has been studied in controlled situations, including the treatment of diabetic ulcers, infected deep wounds following heart surgery, and wounds of lepers. The treatment eradicates bacterial infections better than some antiseptics, and accelerates healing without scarring, or with minimal scarring. The sugar regulates the communication between cells, and optimizes the synthesis of collagen and extracellular matrix.

An excess of insulin, causing hypoglycemia, can cause blood vessels, for example in the brain and kidneys, to become leaky, and this has been claimed to be an effect of insulin itself. However, the same leakiness can be produced by an analog of glucose that can't be metabolized, so that intracellular glycopenia is produced. The harmful effect that has been ascribed to excessive insulin can be prevented by maintaining an adequate supply of glucose (Uezu and Murakami, 1993), showing that it is the lack of glucose, rather than the excess insulin, that causes the vascular malfunction. Fructose also reduces the leakiness of blood vessels (Plante, et al., 2003). Many of the complications of diabetes are caused by increased vascular leakiness (Simard, et al., 2002).

Sugar can protect the beta-cells from the free fatty acids, apparently in the same ways that it protects the cells of blood vessels, restoring metabolic energy and preventing damage to the mitochondria. Glucose suppresses superoxide formation in beta-cells (Martens, et al., 2005) and apparently in other cells including brain cells. (Isaev, et al., 2008).

The beta-cell protecting effect of glucose is supported by bicarbonate and sodium. Sodium activates cells to produce carbon dioxide, allowing them to regulate calcium, preventing overstimulation and death. For a given amount of energy released, the oxidation of glucose produces more carbon dioxide and uses less oxygen than the oxidation of fatty acids.

The toxic excess of intracellular calcium that damages the insulin-secreting cells in the relative absence of carbon dioxide is analogous to the increased excitation of nerves and muscles that can be produced by hyperventilation.

In every type of tissue, it is the failure to oxidize glucose that produces oxidative stress and cellular damage. Even feeding enough sucrose to cause fat deposition in the liver can protect the liver from oxidative stress (Spolarics and Meyenhofer, 2000), possibly by mechanisms such as those involved in the treatment of alcoholic liver disease with saturated fats.

The active thyroid hormone, T3, protects the heart by supporting the oxidation of glucose (Liu, et al., 1998). The amount of T3 produced by the liver depends mainly on the amount of glucose available.

Animals that have been made diabetic with relatively low doses of the poison streptozotocin can recover functional beta-cells spontaneously, and the rate of recovery is higher in pregnant animals (Hartman, et al., 1989). Pregnancy stabilizes blood sugar at a higher level, and

progesterone favors the oxidation of glucose rather than fats.

A recent study suggests that recovery of the pancreas can be very fast. A little glucose was infused for 4 days into rats, keeping the blood glucose level normal, and the mass of beta-cells was found to have increased 2.5 times. Cell division wasn't increased, so apparently the additional glucose was preventing the death of beta-cells, or stimulating the conversion of another type of cell to become insulin-secreting beta-cells (Jetton, et al., 2008).

That study is very important in relation to stem cells in general, because it either means that glandular cells are turning over ("streaming") at a much higher rate than currently recognized in biology and medicine, or it means that (when blood sugar is adequate) stimulated cells are able to recruit neighboring cells to participate in their specialized function. Either way, it shows the great importance of environmental factors in regulating our anatomy and physiology.

"Diabetologists" don't regularly measure their patients' insulin, but they usually make the assumption that insulin is the main factor regulating blood sugar. In one study, it was found that the insulin molecule itself, immunoreactive insulin, accounted for only about 8% of the serum's insulin-like action. The authors of that study believed that potassium was the main other factor in the serum that promoted the disposition of glucose. Since potassium and glucose are both always present in the blood, their effects on each other have usually been ignored.

Cellular activation (by electrical, nervous, chemical, or mechanical stimulation) causes glucose to be absorbed and oxidized, even in the absence of insulin and in otherwise insulin-resistant individuals. I think this local interaction between the need for energy and the production of energy predominates in good health, with insulin and other hormones facilitating the process in times of stress. A variety of local tissue regulators, including GABA and glutamate, probably participate in these interactions, in the brain, endocrine glands, muscles, and other tissues, and are probably involved in the relaxing and analgesic actions of the sugars.

The GABA system (GABA is highly concentrated in the beta-cells) is involved in regulating blood sugar, inhibiting the release of glucagon when glucose isn't needed, and apparently allowing the beta cells to discriminate between amino acids and glucose (Gu, et al., 1993) and acting as a survival and growth factor for neighboring cells (Ligon, et al., 2007).

The damaged beta-cells lose the enzyme (glutamate dehydrogenase) that makes GABA, and their ratio of linoleic acid to saturated and monounsaturated fat increases, a change that corresponds to a decreased metabolism of glucose.

The free intracellular calcium that can become toxic is normally bound safely by well-energized mitochondria, and in the bloodstream it is kept safely complexed with carbon dioxide. The thyroid hormone, producing carbon dioxide, helps to sustain the level of ionized calcium (Lindblom, et al., 2001). In a vitamin D deficiency, or a calcium deficiency, the parathyroid hormone increases, and this hormone can contribute to many inflammatory and degenerative processes, including diabetes. Consuming enough calcium and vitamin D to keep the parathyroid hormone suppressed is important to protect against the degenerative conditions.

When animals were fed an otherwise balanced diet lacking vitamin D, with the addition of either 68% sucrose or 68% starch, the bones of those on the starch diet failed to develop normally, as would be expected with a vitamin D deficiency, and their serum calcium was low. However, the bones of those on the diet with sucrose developed properly, and didn't show evidence of being calcium deficient, though they weren't quite as heavy as those that also received an adequate amount of vitamin D (Artus, 1975). This study suggests that the famous dietetic emphasis on the "complex carbohydrates," i.e., starches, has made an important contribution to the prevalence of osteoporosis, as well as obesity and other degeneration conditions.

Both vitamin D and vitamin K, another important calcium-regulating nutrient, are now known to prevent diabetes. Both of these vitamins require carbon dioxide for disposing of calcium properly,

preventing its toxicity. When carbon dioxide is inadequate, for example from simple hyperventilation or from hypothyroidism, calcium is allowed to enter cells, causing inappropriate excitation, sometimes followed by calcification.

Keeping an optimal level of carbon dioxide (for example, when adapted to high altitude) causes calcium to be controlled, resulting in lowered parathyroid hormone, an effect similar to supplementing with calcium, vitamin D, and vitamin K. (E.g., Nicolaidou, et al, 2006.) Glycine, like carbon dioxide, protects proteins against oxidative damage (Lezcano, et al., 2006), so including gelatin (very rich in glycine) in the diet is probably protective.

The contribution of PTH to inflammation and degeneration is just being acknowledged (e.g., Kuwabara, 2008), but the mechanism undoubtedly involves the fact that it is lipolytic, increasing the concentration of free fatty acids that suppress metabolism and interfere with the use of glucose.

When we talk about increasing the metabolic rate, and the benefits it produces, we are comparing the rate of metabolism in the presence of thyroid, sugar, salt, and adequate protein to the "normal" diet, containing smaller amounts of those "stimulating" substances. It would be more accurate if we would speak of the suppressive nature of the habitual diet, in relation to the more optimal diet, which provides more energy for work and adaptation, while minimizing the toxic effects of free radicals.

Feeding animals a normal diet with the addition of Coca-Cola, or with a similar amount of sucrose, has been found to let them increase their calorie intake by 50% without increasing their weight gain (Bukowiecki, et al., 1983). Although plain sucrose can alleviate the metabolic suppression of an average diet, the effect of sugars in the diet is much more likely to be healthful in the long run when they are associated with an abundance of minerals, as in milk and fruit, which provide potassium and calcium and other protective nutrients.

Avoiding the starches such as cereals and beans, and using fruits as a major part of the diet helps to minimize the effects of the polyunsaturated fats.

Celiac disease or gluten sensitivity is associated with diabetes and hypothyroidism. There is a cross reactivity between the gluten protein molecule and an enzyme which is expressed under the influence of estrogen. This is another reason for simply avoiding cereal products.

Brewers' yeast has been used traditionally to correct diabetes, and its high content of niacin and other B vitamins and potassium might account for its beneficial effects. However, eating a large quantity of it is likely to cause gas, so some people prefer to extract the soluble nutrients with hot water. Yeast contains a considerable amount of estrogen, and the water extract probably leaves much of that in the insoluble starchy residue. Liver is another rich source of the B vitamins as well as the oily vitamins, but it can suppress thyroid function, so usually one meal a week is enough.

The supplements that most often help to correct diabetes-like conditions are niacinamide, thiamine, thyroid, and progesterone or pregnenolone. Vitamins D and K are clearly protective against developing diabetes, and their effects on many regulatory processes suggest that they would also help to correct existing hyperglycemia.

Drinking coffee seems to be very protective against developing diabetes. Its niacin and magnesium are clearly important, but it is also a rich source of antioxidants, and it helps to maintain normal thyroid and progesterone production. Chocolate is probably protective too, and it is a good source of magnesium and antioxidants.

A recent study (Xia, et al., 2008) showed that inhibition of cholesterol synthesis by beta-cells impairs insulin synthesis, and that replenishing cholesterol restores the insulin secretion. Green tea contains this type of inhibitor, but its use has nevertheless been associated with a reduced risk of diabetes. Caffeine is likely to be the main protective substance in these foods.

Although antioxidants can be protective against diabetes, not all things sold as "antioxidants" are safe; many botannical "antioxidants" are estrogenic. Hundreds of herbal products can lower blood sugar, but many of them are simply toxic, and the reduction of blood glucose can make some problems worse.

The supplements I mention above--including caffeine--have antiinflammatory, antioxidative and energy-promoting effects. Inflammation, interfering with cellular energy production, is probably the essential feature of the things called diabetes.

Aspirin has a very broad spectrum of antiinflammatory actions, and is increasingly being recommended for preventing complications of diabetes. One of the consequences of inflammation is hyperglycemia, and aspirin helps to correct that (Yuan, et al., 2001), while protecting proteins against oxidative damage (Jafarnejad, et al, 2001).

If Dr. Budd's thinking (and results) had been more widely accepted when his publications appeared, thinking about "diabetes" might have led to earlier investigation of the syndromes of stress and tissue wasting, with insulin being identified as just one of many regulatory substances, and a large amount of useless and harmful activity treating hyperglycemia as the enemy, rather than part of an adaptive reaction, might have been avoided.

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Ray Peat's Newsletter

Every Man's Wisdom is peculiar to his own Individuality. **W. Blake**

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Protective CO2 and aging

The therapeutic effects of increasing carbon dioxide are being more widely recognized in recent years. Even Jane Brody, the NY Times writer on health topics, has favorably mentioned the use of the Buteyko method for asthma, and the idea of "permissive hypercapnia" during mechanical ventilation, to prevent lung damage from excess oxygen, has been discussed in medical journals. But still very few biologists recognize its role as a fundamental, universal protective factor. I think it will be helpful to consider some of the ways carbon dioxide might be controlling situations that otherwise are poorly understood.

The brain has a high rate of oxidative metabolism, and so it forms a very large proportion of the carbon dioxide produced by an organism. It also governs, to a great extent, the metabolism of other tissues, including their consumption of oxygen and production of carbon dioxide or lactic acid. Within a particular species, the rate of oxygen consumption increases in proportion to brain size, rather than body weight. Between very different species, the role of the brain in metabolism is even more obvious, since the resting metabolic rate corresponds to the size of the brain. For example, a cat's brain is about the size of a crocodile's, and their oxygen consumption at rest is similar, despite their tremendous difference in body size.

Stress has to be understood as a process that develops in time, and the brain (especially the neocortex and the frontal lobes) organizes the adaptive and developmental processes in both the spatial and temporal dimensions. The meaning of a situation influences the way the organism responds. For example, the stress of being restrained for a long time can cause major gastrointestinal bleeding and ulcerization, but if the animal has the opportunity to bite something during the stress (signifying its ability to fight back, and the possibility of escape) it can avoid the stress ulcers.

The patterning of the nervous activity throughout the body governs the local ability to produce carbon dioxide. When the cortex of the brain is damaged or removed, an animal becomes rigid, so the cortex is considered to have a "tonic inhibitory action" on the body. But when the nerves are removed from a muscle (for example, by disease or accident), the muscle goes into a state of constant activity, and its ability to oxidize glucose and produce carbon dioxide is reduced, while its oxidation of fatty acids persists, increasing the production of toxic oxidative fragments of the fatty acids, which contributes to the muscle's atrophy.

The organism's intentions, expectations, or plans, are represented in the nervous system as a greater readiness for action, and in the organs and tissues controlled by the nerves, as an increase or decrease of oxidative efficiency, analogous to the differences between innervated and denervated muscles. This pattern in the nervous system has been called "the acceptor of action," because it is continually being compared with the actual situation, and being refined as the situation is evaluated. The state of the organism, under the influence of a particular acceptor of action, is called a "functional system," including all the components of the organism that participate most directly in realizing the intended adaptive action.

The actions of nerves can be considered anabolic, because during a stressful situation in which the catabolic hormones of adaption, e.g., cortisol, increase, the tissues of the functional system are protected, and while idle tissues may undergo autophagy or other form of involution, the needs of the active tissues are supplied with

nutrients from their breakdown, allowing them to change and, when necessary, grow in size or complexity.

The brain's role in protecting against injury by stress, when it sees a course of action, has a parallel in the differences between concentric (positive, muscle shortening) and eccentric (negative, lengthening under tension) exercise, and also with the differences between innervated and denervated muscles. In eccentric exercise and denervation, less oxygen is used and less carbon dioxide is produced, while lactic acid increases, displacing carbon dioxide, and more fat is oxidized. Prolonged stress similarly decreases carbon dioxide and increases lactate, while increasing the use of fat.

Darkness is stressful and catabolic. For example, in aging people, the morning urine contains nearly all of the calcium lost during the 24 hour period, and mitochondria are especially sensitive to the destructive effects of darkness. Sleep reduces the destructive catabolic effects of darkness. During the rapid-eye-movement (dreaming) phase of sleep, breathing is inhibited, and the level of carbon dioxide in the tissues accumulates. In restful sleep, the oxygen tension is frequently low enough, and the carbon dioxide tension high enough, to trigger the multiplication of stem cells and mitochondria.

Dreams represent the "acceptor of action" operating independently of the sensory information that it normally interacts with. During dreams, the brain (using a system called the Ascending Reticular Activating System) disconnects itself from the sensory systems. I think this is the nervous equivalent of concentric/positive muscle activity, in the sense that the brain is in control of its actions. The active, dreaming phase of sleep occurs more frequently in the later part of the night, as morning approaches. This is the more stressful part of the night, with cortisol and some other stress hormones reaching a peak at dawn, so it would be reasonable for the brain's defensive processes to be most active at that time. The dreaming process in the brain is associated with deep muscle relaxation, which is probably associated with the trophic (restorative) actions of the nerves.

In ancient China the Taoists were concerned with longevity, and according to Joseph Needham (*Science and Civilization in China*) their methods included the use of herbs, minerals, and steroids extracted from the urine of children. Some of those who claimed extreme longevity practiced controlled breathing and tai chi (involving imagery, movement, and breating), typically in the early morning hours, when stress reduction is most important. As far as I know, there are no studies of carbon dioxide levels in practitioners of tai chi, but the sensation of warmth they typically report suggests that it involves hypoventilation.

In the 1960s, a Russian researcher examined hospital records of measurements of newborn babies, and found that for several decades the size of their heads had been increasing. He suggested that it might be the result of increasing atmospheric carbon dioxide.

The experiences and nutrition of a pregnant animal are known to affect the expression of genes in the offspring, affecting such things as allergies, metabolic rate, brain size, and intelligence. Miles Storfer (1999) has reviewed the evidence for epigenetic environmental control of brain size and intelligence. The main mechanisms of epigenetic effects or "imprinting" are now known to involve methylation and acetylation of the chromosomes (DNA and histones).

Certain kinds of behavior, as well as nutrition and other environmental factors, increase the production and retention of carbon dioxide. The normal intrauterine level of carbon dioxide is high, and it can be increased or decreased by changes in the mother's physiology. The effects of carbon dioxide on many biological processes involving methylation and acetylation of the genetic material suggest that the concentration of carbon dioxide during gestation might regulate the degree to which parental imprinting will persist in the developing fetus. There is some evidence of increased demethylation associated with the low level of oxygen in the uterus (Wellman, et al., 2008). A high metabolic rate and production of carbon dioxide would increase the adaptability of the new organism, by decreasing the limiting genetic imprints.

A quick reduction of carbon dioxide caused by hyperventilation can provoke an epileptic seizure, and can increase muscle spasms and vascular leakiness, and (by releasing serotonin and histamine) contribute to inflammation and clotting disorders. On a slightly longer time scale, a reduction of carbon dioxide can increase the production of lactic acid, which is a promoter of inflammation and fibrosis. A prolonged decrease in carbon dioxide can increase the susceptibility of proteins to glycation (the addition of aldehydes, from polyunsaturated fat peroxidation or methylglyoxal from lactate metabolism, to amino groups), and a similar process is likely to contribute to the methylation of histones, a process that increases with aging. Histones regulate genetic activity.

With aging, DNA methylation is increased (Bork, et al., 2009). **I suggest that methylation stabilizes and protects cells when growth and regeneration aren't possible (and that it's likely to increase when CO2 isn't available).** Hibernation (Morin and Storey, 2009) and sporulation (Ruiz-Herrera, 1994; Clancy, et al., 2002) appear to use methylation protectively.

Parental stress, prenatal stress, early life stress, and even stress in adulthood contribute to "imprinting of the genes," partly through methylation of DNA and the histones.

Methionine and choline are the main dietary sources of methyl donors. Restriction of methionine has many protective effects, including increased average (42%) and maximum (44%) longevity in rats (Richie, et al., 1994). Restriction of methyl donors causes demethylation of DNA (Epner, 2001). The age accelerating effect of methionine might be related to disturbing the methylation balance, inappropriately suppressing cellular activity. Besides its effect on the methyl pool, methionine inhibits thyroid function and damages mitochondria.

The local concentration of carbon dioxide in specific tissues and organs can be adjusted by nervous and hormonal activation or inhibition of the carbonic anhydrase enzymes, that accelerate the oonversion of CO2 to carbonic acid, H2CO3. The activity of carbonic anhydrase can determine the density and strength of the skeleton, the excitability of nerves, the accumulation of water, and can regulate the structure and function of the tissues and organs.

Ordinarily, carbon dioxide and bicarbonate are thought of only in relation to the regulation of pH, and only in a very general way. Because of the importance of keeping the pH of the blood within a narrow range, carbon dioxide is commonly thought of as a toxin, because an excess can cause unconsciousness and acidosis. But increasing carbon dioxide doesn't necessarily cause acidosis, and acidosis caused by carbon dioxide isn't as harmful as lactic acidosis.

Frogs and toads, being amphibians, are especially dependent on water, and in deserts or areas with a dry season they can survive a prolonged dry period by burrowing into mud or sand. Since they may be buried 10 or 11 inches below the surface, they are rarely found, and so haven't been extensively studied. In species that live in the California desert, they have been known to survive 5 years of burial without rainfall, despite a moderately warm average temperature of their surroundings. One of their known adaptations is to produce a high level of urea, allowing them to osmotically absorb and retain water. (Very old people sometimes have extremely high urea and osmotic tension.)

Some laboratory studies show that as a toad burrows into mud, the amount of carbon dioxide in its tissues increases. Their skin normally functions like a lung, exchanging oxygen for carbon dioxide. If the toad's nostrils are at the surface of the mud, as dormancy begins its breathing will gradually slow, increasing the carbon dioxide even more. Despite the increasing carbon dioxide, the pH is kept stable by an increase of bicarbonate (Boutilier, et al., 1979). A similar increase of bicarbonate has been observed in hibernating hamsters and doormice.

Thinking about the long dormancy of frogs reminded me of a newspaper story I read in the 1950s. Workers breaking up an old concrete structure found a dormant toad enclosed in the concrete, and it revived soon after being released. The concrete had been poured decades earlier.

Although systematic study of frogs or toads during their natural buried estivation has been very limited, there have been many reports of

accidental discoveries that suggest that the dormant state might be extended indefinitely if conditions are favorable. Carbon dioxide has antioxidant effects, and many other stabilizing actions, including protection against hypoxia and the excitatory effects of intracellular calcium and inflammation (Baev, et al., 1978, 1995; Bari, et al., 1996; Brzecka, 2007; Kogan, et al., 1994; Malyshev, et al., 1995).

When mitochondria are "uncoupled," they produce more carbon dioxide than normal, and the mitochondria produce fewer free radicals. Animals with uncoupled mitochondria live longer than animals with the ordinary, more efficient mitochondria, that produce more reactive oxidative fragments. One effect of the high rate of oxidation of the uncoupled mitochondria is that they can eliminate polyunsatured fatty acids that might otherwise be integrated into tissue structures, or function as inappropriate regulatory signals.

Birds have a higher metabolic rate than mammals of the same size, and live longer. Their tissues contain fewer of the highly unsaturated fatty acids. Queen bees, which live many times longer than worker bees, have mainly monounsaturated fats in their tissues, while the tissues of the short-lived worker bees, receiving a different diet, within a couple of weeks of hatching will contain highly unsaturated fats.

Bats have a very high metabolic rate, and an extremely long lifespan for an animal of their size. While most animals of their small size live only a few years, many bats live a few decades. Bat caves usually have slightly more carbon dioxide than the outside atmosphere, but they usually contain a large amount of ammonia, and bats maintain a high serum level of carbon dioxide, which protects them from the otherwise toxic effects of the ammonia.

The naked mole rat, another small animal with an extremely long lifespan (in captivity they have lived up to 30 years, 9 or 10 times longer than mice of the same size) has a low basal metabolic rate, but I think measurements made in laboratories might not represent their metabolic rate in their natural habitat. They live in burrows that are kept closed, so the percentage of oxygen is lower than in the outside air, and the percentage of carbon dioxide ranges from 0.2% to 5% (atmospheric CO2 is about 0.038%). The temperature and humidity in their burrows can be extremely high, and to be very meaningful their metabolic rate would have to be measured when their body temperature is raised by the heat in the burrow.

When they have been studied in Europe and the US, there has been no investigation of the effect of altitude on their metabolism, and these animals are native to the high plains of Kenya and Ethiopia, where the low atmospheric pressure would be likely to increase the level of carbon dioxide in their tissues. Consequently, I doubt that the longevity seen in laboratory situations accurately reflects the longevity of the animals in their normal habitat.

Besides living in a closed space with a high carbon dioxide content, mole rats have another similarity to bees. In each colony, there is only one female that reproduces, the queen, and, like a queen bee, she is the largest individual in the colony. In beehives, the workers carefully regulate the carbon dioxide concentration, which varies from about 0.2% to 6%, similar to that of the mole rat colony. A high carbon dioxide content activates the ovaries of a queen bee, increasing her fertility.

Since queen bees and mole rats live in the dark, I think their high carbon dioxide compensates for the lack of light. (Both light and CO2 help to maintain oxidative metabolism and inhibit lactic acid formation.) Mole rats are believed to sleep very little. During the night, normal people tolerate more CO2, and so breathe less, especially near morning, with increased active dreaming sleep.

A mole rat has never been known to develop cancer. Their serum C-reactive protein is extremely low, indicating that they are resistant to inflammation. In humans and other animals that are susceptible to cancer, one of the genes that is likely to be silenced by stress, aging, and methylation is p53, a tumor-suppressor gene.

If the intrauterine experience, with low oxygen and high carbon dioxide, serves to "reprogram" cells to remove the accumulated effects of

age and stress, and so to maximize the developmental potential of the new organism, a life that's lived with nearly those levels of oxygen and carbon dioxide might be able to avoid the progressive silencing of genes and loss of function that cause aging and degenerative diseases.

Several diseases and syndromes are now thought to involve abnormal methylation of genes. Prader-Willi sydrome, Angelman's syndrome, and various "autistic spectrum disorders," as well as post-traumatic stress disorder and several kinds of cancer seem to involve excess methylation.

Moderate methionine restriction (for example, using gelatin regularly in the diet) might be practical, but if increased carbon dioxide can activate the demethylase enzymes in a controlled way, it might be a useful treatment for the degenerative diseases and for aging itself.

The low carbon dioxide production of hypothyroidism (e.g., Lee and Levine, 1999), and the respiratory alkalosis of estrogen excess, are often overlooked. An adequate supply of calcium, and sometimes supplementation of salt and baking soda, can increase the tissue content of CO2.

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Can J Anaesth. 1999 Feb;46(2):185-9. **Acute respiratory alkalosis associated with low minute ventilation in a patient with severe hypothyroidism.** Lee HT, Levine M. Tl128@columbia.edu PURPOSE: Patients with severe hypothyroidism present unique challenges to anesthesiologists and demonstrate much increased perioperative risks. Overall, they display

increased sensitivity to anesthetics, higher incidence of perioperative cardiovascular morbidity, increased risks for postoperative ventilatory failure and other physiological derangements. The previously described physiological basis for the increased incidence of postoperative ventilatory failure in hypothyroid patients includes decreased central and peripheral ventilatory responses to hypercarbia and hypoxia, muscle weakness, depressed central respiratory drive, and resultant alveolar hypoventilation. These ventilatory failures are associated most frequently with severe hypoxia and carbon dioxide (CO2) retention. The purpose of this clinical report is to discuss an interesting and unique anesthetic presentation of a patient with severe hypothyroidism. CLINICAL FEATURES: We describe an unique presentation of ventilatory failure in a 58 yr old man with severe hypothyroidism. He had exceedingly low perioperative respiratory rate (3-4 bpm) and minute ventilation volume, and at the same time developed primary acute respiratory alkalosis and associated hypocarbia (P(ET)CO2 approximately 320-22 mmHg). CONCLUSION: Our patient's ventilatory failure was based on unacceptably low minute ventilation and respiratory rate that was unable to sustain adequate oxygenation. His profoundly lowered basal metabolic rate and decreased CO2 production, resulting probably from severe hypothyroidism, may have resulted in development of acute respiratory alkalosis in spite of concurrently diminished minute ventilation.

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Ray Peat's Newsletter

The best way out is always through. Robert Frost

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Cascara, energy, cancer and the FDA's laxative abuse

The medical culture and the general culture share some attitudes about the nature of the most common ailments--colds, cancer, arthritis, constipation, heart problems, etc., and they often agree about which things can be treated at home, and which require special medical care.

These background ideas are important because they influence the actions of insurance companies, legislators, and regulatory agencies. They also influence the judgments people make about their own health, and, too often, the way physicians treat their patients.

The prevalence of chronic constipation in North America has been estimated to be 27%, and in a ten year study, the occurrence of new cases was about 16%.--the prevalence increases with aging. In some studies, women are 3 times as likely as men to suffer from constipation. A recent Canadian article commented that "While chronic constipation (CC) has a high prevalence in primary care, there are no existing treatment recommendations to guide health care professionals."

Almost everyone in the US is familiar with the idea of "laxative abuse," of using laxatives when they aren't absolutely necessary, and with the idea that chronic laxative use will create a dependency, the way an addictive drug does. Contemporary doctors are likely to prescribe stool softeners for constipated old people, rather than "stimulant laxatives," probably because "softener" doesn't have the pejorative connotation that "stimulant drug" has--not because there is a scientific basis for the choice.

Many doctors advise constipated patients to drink more water and exercise. While there is some physiological basis for recommending exercise, the advice to drink more water is simply unphysiological. A study in Latin America found no evidence of benefit from either of those recommendations, and recommended the use of fiber in the diet. The right kind of fiber can benefit a variety of bowel problems. However, some types of fiber can exacerbate the problem, and some types (such as oat bran) have been found to increase bowel cancer in animal studies.

Despite the greater prevalence of constipation in women and older people, even specialists in gastroenterology are very unlikely to consider the role of hypothyroidism or other endocrine problems in chronic constipation.

Because of the cultural clichés about constipation--that it's caused by not eating enough fiber or drinking enough water, for example--and the belief that it's not very important, there is seldom an effort made to understand the actual condition of the intestine, and the causes of the problem.

Aging and stress increase some of the inflammatory mediators, tending to reduce the barrier function of the bowel, letting larger amounts of bacterial toxins enter the bloodstream, interfering with energy metabolism, creating inflammatory vicious circles of increasing leakiness and inflammation.

Often people visualize something like a sausage casing when they think of the intestine, but when the intestine is becoming inflamed its wall may swell to become an inch thick. As it thickens, the channel narrows to a few millimeters in diameter, and may even close in some regions. In the swollen, edematous, inflamed condition the contractile mechanism of the smooth muscle is impaired. The failure of contraction is caused by the same structural changes that increase permeability. (Garcia, et al., 1996; Skarsgard, et al., 2000; Plaku and von der Weid, 2006; Uray, et al.,

2006; Miller and Sims, 1986; Schouten, et al., 2008; Gosling, et al., 2000.)

Obviously, in the very swollen, structurally deformed intestine, with almost no lumen, neither a stimulant nor a simple fibrous bulk could restore functioning, because even with stimulation the smooth muscle is unable to contract, and the closed channel won't admit bulk. Even gas is sometimes unable to pass through the inflamed intestine. Mechanical thinking about the intestine fails when inflammation is involved; now that inflammation is known to play an important role in Alzheimer's disease and heart disease, it will be more acceptable to consider its role in constipation.

The contractile ability of smooth muscle, that's impaired by swelling and inflammation, can be restored by antiinflammatory agents, for example aspirin (or other inhibitor of prostaglandin synthesis) or antihistamines. This applies to the muscles of lymphatic vessels (Wu, et al., 2005, 2006; Gosling, 2000), that must function to reduce edema, as well as to the bowel muscles that cause peristalsis.

If someone thinks of constipation as the result of a lack of neuromuscular stimulation, then it might seem reasonable to design a drug that intensifies the contractions produced by one of the natural transmitter substances, such as serotonin, histamine, or acetylcholine. That's apparently what Novartis did, with tegaserod, a drug that increases the bowel's sensitivity to serotonin. That drug, called Zelnorm, was approved by the FDA in 2002, after a couple of years of publications praising it. At the time of its approval, there was already evidence that people using it were more likely to have abdominal surgery, especially for gallbladder disease, and there was doubt about its effectiveness.

Strangely, the drug was approved to be used for only 4 to 6 weeks, taking two tablets daily without interruption. When patients benefitted from the first treatment, they might be eligible for an additional 4 to 6 weeks, but then it would be necessary for them to find another way to deal with their constipation.

Zelnorm side effects: abdominal pain, chest pain, flushing, facial edema, hypertension, hypotension, angina pectoris, syncope, arrythmia, anxiety, vertigo, ovarian cyst, miscarriage, menorrbagia, cholecystitis, appendicitis, bilirubinemia, gastroenteritis, increased creatine phosphokinase. back pain, cramps, **breast cancer, attempted suicide,** impaired concentration, increased appetite, sleep disorder, depression, anxiety, asthma, increased sweating, renal pain, polyuria. (Later, it was found to cause heart attacks and intestinal ischemia/necrosis.) Why would the FDA approve a drug, without evidence that it was more effective than harmless things that were already widely available?

Zelnorm Prices ~ In the US, Novartis estimates that Zelnorm tablets will sell for somewhere in the range of $3 to $4 each. The drug is expected to generate $1 billion in annual sales for Novartis.

During the years just before the new drug was approved, there were several publications reporting that emodin, the main active factor in cascara, a traditional laxative, had some remarkable antiviral and anticancer activities. Other studies were reporting that it protected against some known mutagens and carcinogens. Less than 3 months before approving Zelnorm, the FDA announced its Final rule [Federal Register: May 9, 2002 (Volume 67, Number 90)] "Certain Additional Over-the-Counter Drug Category II and III Active Ingredients." "the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract)," determining that they "are not generally recognized as safe and effective or are misbranded. This final rule is part of FDA's ongoing OTC drug product review. This rule is effective November 5, 2002."

Historically, the FDA has ruled against traditional generic drug products when the drug industry is ready to market a synthetic substitute product.

In 2007, the FDA withdrew its approval for Zelnorm, but allowed it to be licensed as an "Investigational New Drug." *"On April 2, 2008, after more than eight months of availability, the company has re-assessed the program and has made a decision to close it. Novartis is in the process of communicating this decision to physicians participating in the program. Patients who had access to Zelnorm via this program are instructed to discuss alternative treatment options with their physicians."*

Cascara and aloe are not among the treatment options approved by the FDA, so cascara isn't

widely available (though anyone can grow aloe plants easily). However, there is considerable interest in the drug industry in the possibility of developing products based on emodin, or aloe-emodin, as anticancer or antiviral drugs. Even if it were proved to be safe and effective for use as a laxative, its potential use as an alternative to extremely profitable cancer and virus treatments would make it a serious threat to the drug industry.

Although the standard medical journals have only recently begun writing about it as a cancer treatment, emodin and related chemicals have been of interest as a non-toxic way to treat cancer, allergies, and viral and bacterial diseases for a long time.

In 1900, Moses Gomberg demonstrated the synthesis of a stable free radical (triphenylmethyl), but for years many chemists believed free radicals couldn't exist. A student of Gomberg's, William F. Koch, came to believe that cellular respiration involved free radicals, and experimented with the metabolic effects of many organic molecules, quinones of several kinds, that can form free radicals, looking for the most useful ones.

For more than 50 years the U.S. Government and the main medical instititutions actively fought the idea that a free radical or quinone could serve as a biological catalyst to correct a wide variety of health problems.

A free radical has an unpaired electron. In 1944 Yevgeniy Zavoisky devised a way to measure the behavior of unpaired electrons in crystals, but it was many years before it was recognized that they are essential to cellular respiration. Alex Comfort demonstrated them in living tissue in 1959.

By the time coenzyme Q_{10}, ubiquinone, was officially discovered, Koch had moved to Brazil to continue his work with the biological effects of the quinones, including the anthraquinone compound of brazilwood, which is used as a dye. He also used a naphthoquine, lapachone. Although vitamin K was identified as a quinone (naphthoquinone) not long after coQ_{10} was found to be a ubiquitous component of the mitochondrial respiratory system, it wasn't immediately recognized as another participant in that system, interacting with coQ_{10}.

Although Koch was unable to publish in any English language medical journal after 1914, his work was widely known. In the 1930s, Albert Szent-Gyorgyi, following Koch's ideas about electrons in cells, interacting with free radicals, began working on the links between electronic energy and cellular movement. Since free (or relatively free) electrons absorb light, Szent-Gyorgyi worked with many colorful substances. When he came to the US in 1947, and wanted to expand his research, a team of professors from Harvard investigated, and told the government funding agency that his work didn't deserve support. For the rest of his life, he worked on related ideas, expanding ideas that Koch had first developed.

Emodin and the anthraquinones (and naphthoquinones, such as lapachone) weren't the reagents that Koch considered the most powerful, but emodin can produce to some degree all of the effects that he believed could be achieved by correcting the cellular respiratory apparatus: Antiinflammatory, antifibrotic (Wang, et al., 2007) antiviral, antidepressant, heart protective, antioxidant, memory enhancing, anticancer, anxiolytic and possibly antipsychotic.

Working backward from these effects, we get a better perspective on the "laxative" function of emodin and cascara. Koch and Szent-Gyorgyi believed that cellular movement and secretion were electronically regulated. In one of his demonstrations, Szent-Gyorgyi showed that muscles could be caused to contract when they were exposed to two substances which, when combined, partially exchange an electron, causing an intense color reaction, but without causing an ordinary chemical (oxidation-reduction) reaction. This kind of reaction is called a Donor-Acceptor reaction, and it is closely related to the phenomenon of semiconduction. The reacting molecules have to be exactly "tuned" to each other, allowing an electron to resonate between the molecules.

In a muscle, any D-A matched pair of molecules would cause a contraction, but the same molecules, combined in pairs that weren't exactly tuned to each other, failed to cause contraction. Szent-Gyorgyi believed that biological signal

substances operated in a similar way, by adjusting the electronic balance of cellular proteins.

An effective laxative (besides preventing inflammation) causes not only coordinated contraction of the smooth muscles of the intestine, but also adjusts secretions and absorption, so that an appropriate amount of fluid stays in the intestine, and the cells of the intestine don't become water-logged.

In the presence of bacterial endotoxin, respiratory energy production fails in the cells lining the intestine. Nitric oxide is probably the main mediator of this effect.

The shift from respiration to glycolysis, from producing carbon dioxide to producing lactic acid, involves a global change in cell functions, away from specialized differentiated functioning, toward defensive and inflammatory processes.

This global change involves a change in the physical properties of the cytoplasm, causing a tendency to swell, and to admit dissolved substances that normally wouldn't enter the cells.

The interface between the cells lining the intestine and the bacteria-rich environment involves processes similar to those in cells at other interfacial situations throughout the body--kidney, bladder, secretory membranes of glands, capillary cells, etc. The failure of the intestinal barrier is especially dangerous, because of the generalized toxic consequences, but the principles of maintaining and restoring it are general, and they have to do with the nature of life.

Some leakage from the lumen of the intestine or the lumen of a blood vessel can occur between cells, but it is often claimed that the "paracellular" route accounts for all leakage. (Anthraquinones may inhibit paracellular leakage [Karbach & Wanitschke, 1984].) When a cell is inflamed or overstimulated or fatigued, its cytoplasmic contents leak out. In that state, its barrier function is weakened, and external material can leak in. This was demonstrated long ago by Nasonov, but the "membrane" doctrine is incompatible with the facts, so the paracellular route is claimed to explain leakage. Since the cells that form the barrier begin to form regulatory substances such as nitric oxide when they are exposed to endotoxin, it is clear that major metabolic and energetic changes coincide in the cell with the observed leakiness. Permeability varies with the nature of the substance, its oil and water solubility, and the direction of its movement, arguing clearly that it isn't a matter of mere holes between cells.

Besides endotoxin, estrogen, vibrational injury, radiation, aging, cold, and hypoosmolarity, increase NO synthesis and release, and increase cellular permeabilities throughout the body.

Estrogen excess (relative to progesterone and androgens), as in pregnancy, stress, and aging, reduces intestinal motility, probably by increasing nitric oxide production. The anthraquinones inhibit the formation of nitric oxide, which is constantly being promoted by endotoxin.

Cells regulate their water content holistically, and, to a great extent, autonomously, by adjusting their structural proteins and their metabolism, but in the process they communicate with surrounding cells and with the organism as a whole, and consequently they will receive various materials needed to improve their stability, by adjusting their energy production, sensitivity, and structural composition.

When these intrinsic corrective processes are inadequate, as in hypothyroidism, with increased estrogen and serotonin, extrinsic factors, including special foods and drugs, can reinforce the adaptive mechanisms. These "adaptogens" can sometimes restore the system to perfect functioning, other times they can merely prevent further injury. Sometimes the adaptogens are exactly like those the body normally has, but that are needed in larger amounts during stress. Coenzyme Q_{10}, vitamin K, short-chain fatty acids, ketoacids, niacinamide, and glycine are examples of this sort--they are always present, but increased amounts can improve resistance to stress.

Another kind of adaptogen resembles the body's intrinsic defensive substances, but isn't produced in significant quantities in our bodies. This type includes caffeine and the anthraquinones (such as emodin) and aspirin and other protective substances from plants. These overlap in functions with some of our intrinsic regulatory substances, and can also complement each other's effects.

Emodin inhibits the formation of nitric oxide, increases mitochondrial respiration, inhibits angiogenesis and invasiveness, inhibits fatty acid

synthase (Zhang, et al., 2002), inhibits HER-2 neu and tyrosine phosphorylases (Zhang, et al., 1995, 1999), and promotes cellular differentiation in cancer cells (Zhang, et al., 1995). The anthraquinones, like other antiinflammatory substances, reduce leakage from blood vessels, but they also reduce the absorption of water from the intestine. Reduced water absorption can be seen in a slight shrinkage of cells in certain circumstances, and is probably related to their promotion of cellular differentiation.

All of these are basic antistress mechanisms, suggesting that emodin and the antiinflammatory anthraquinones are providing something central to the life process itself.

Zelnorm was said to "act like serotonin." Serotonin slows metabolism, reduces oxygen consumption, and increases free radicals such as superoxide and nitric oxide; the production of reactive oxygen species is probably an essential part of its normal function. Emodin has an opposing effect, increasing the metabolic rate. It increases mitochondrial oxygen consumption and ATP synthesis, while decreasing oxidative damage (Du and Ko, 2005, 2006; Huang, et al., 1995).

The Zelnorm episode was just an isolated case of a drug company's exploiting cultural beliefs, with the FDA providing a defensive framework, but the contrast between tegaserod and emodin hints at a deeper and more deadly problem.

W.F. Koch's approach to immunity emphasized the role of energy in maintaining the coherence of the organism, in which toxins were oxidized and made nontoxic. There was no emphasis on destruction either of bacteria or of cancer cells, but only of the toxic factors that interfered with respiration. He demonstrated that the udders of healthy cows could contain more bacteria than those with mastitis, but the bacterial toxins were absent after the cows were treated with his catalyst. He identified the "activated carbonyl group" as the essential feature of antibiotics, the same group that makes coenzyme Q_{10} function in the respiratory system.

Koch's understanding of the oxidative apparatus of life, as a matter of electron balances, involved the idea that molecules with a low ionization potential, making them good electron donors, amines specifically, interfered with respiration, while quinones, with a high affinity for electrons, making them electron acceptors, activated respiration. The toxic effects of tryptophan derivatives, indoles, and other amines related to the behavior of their electrons. (Serotonin wasn't known at the time Koch was doing his basic research.) Koch believed that similar electronic functions were responsible for the effects of viruses.

Both chemical and physical interactions of substances cause electrons to shift in each substance, according to its composition. The shift of electrons accounts for the ability of adsorbed molecules or ions to form multiple layers on a surface, and changes in the electrons of a complex biological molecule affect the shape and function not only of that molecule, but of the molecules associated with it. Interactions of the large molecules of cells, and their adsorbed substances, tend toward stable arrangements, or phases. The type of energy production, and the nature of the regulatory molecules that are present, influence the stability of the various states of an organism's cells. (For more information on cooperative adsorption, see www.gilbertling.org.)

Koch and Szent-Gyorgyi were applying to biology and medicine concepts that were simultaneously being developed in metallurgy, electrochemistry, colloid and surface science, and electronics. They were in the scientific mainstream, and it was the medical-pharmaceutical industry that moved away from this kind of exploration of the interactions of substances, electrons, and organisms.

For Koch, antibiotics and anticancer agents weren't necessarily distinct from each other, and would be expected to have other beneficial effects as well.

But an entirely different view of the immune system was taking over the medical culture just as Koch began his research. Mechnikov's morphogenic view, in which the essential function of "the immune system" was to maintain the integrity of the organism, was submerged by Ehrlich's approach, which emphasized killing pathogens, and at the same time, the genetic theory of cancer was replacing the developmental-environmental theory.

Following the early work on the carcinogenicity of estrogens, and the estrogenicity of carcinogens such as polycyclic aromatic hydrocarbons from soot, a few German and French chemists (e.g., Schmidt and the Pullmans) began calculating the high electron densities of highly reactive regions of the anthracene molecule, showing formally why certain molecules are carcinogenic.

At that time, their work was compatible with a developmental view of cancer. But the fact that the polycyclic molecules could interact with the new model of the DNA gene caused the Pullmans' work to be reduced to nothing but a minor theory of mutagenesis.

Anthraquinones, because of the presence of several oxygen molecules, had low electron densities and were stable. The tetracyclines, with related structure, have some similar properties, and are antiinflammatory, as well as antibiotic.

When a polycyclic bacterial antibiotic, adriamycin (later called doxorubicin), was found to be too toxic to use as an antibiotic, the fact that it was toxic to cancer cells caused it to be developed as a cancer drug. It continued to be widely used even after it was found to cause heart failure in many of the "cured" patients, because of its "success" in killing cancer cells.

The fact that many kinds of cancer cells can be killed by emodin makes it slightly interesting as a cancer drug, but its simple generic nature has caused the drug industry to look for a more Ehrlichian magic bullet; for example, they are still looking for ways to keep doxorubicin from destroying the heart.

Emodin isn't a magic bullet (in fact it isn't a bullet/toxin of any sort), but when combined with all the other adaptogens, it does have a place in cancer therapy, as well as in treating many other ailments.

None of the basic metaphors of mainstream medicine--receptors, lock-and-key, membrane pores and pumps--can account for the laxative, anticancer, cell-protective effects of emodin. The new interest in it provides an opportunity to continue to investigate the effects of adjusting the electrical state of the cell substance, building on the foundations created by William F. Koch, Albert Szent-Gyorgyi, and Gilbert Ling.

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Ray Peat's Newsletter

Living is a constant process of deciding what we are going to do. Jose Ortega y Gasset

Radiation and growth: Incoherent imprinting from inappropriate irradiation.

Agence France-Press: The Transportation Security Administration (TSA) began rolling out full-body scanners at US airports in 2007, but stepped up deployment of the devices this year when stimulus funding made it possible to buy another 450 of the advanced imaging technology scanners. Government officials have said that the scanners have been tested and meet safety standards. But Captain David Bates, president of the Allied Pilots Association, which represents pilots at American Airlines, urged members to avoid the full-body scanner. "No pilot at American Airlines should subject themselves to the needless privacy invasion and potential health risks caused by the body scanner," he said in a letter this month, which was obtained by AFP. A group of scientists at the University of California, San Francisco (UCSF) raised concerns about the "potential serious health risks" from the scanners in a letter sent to the White House Office of Science and Technology in April. Biochemist John Sedat and his colleagues said in the letter that most of the energy from the scanners is delivered to the skin and underlying tissue. "While the dose would be safe if it were distributed throughout the volume of the entire body, the dose to the skin may be dangerously high," they wrote. The scientists say the X-rays could pose a risk to everyone from travelers over the age of 65 to pregnant women and their unborn babies, to HIV-positive travelers, cancer patients and men. "Men's sexual organs are exposed to the X-rays. The skin is very thin there," Love explained.

Beginning in 1944, the US government conducted a series of 250 experiments in which large amounts of radioactive material were released into the atmosphere, to study the effects of radioactive isotopes on people, as part of a program to develop weapons that would kill or sterilize populations.

When hydrogen bombs were produced in the 1950s, the US public was told that these weapons would make nuclear war safe, because they were "clean," since fusion didn't produce the toxic isotopes produced by fission bombs. However, immense quantities of natural uranium 238 were included in those bombs, with the result that they produced extremely radioactive fallout. This was kept secret from Americans, but the Soviets were able to determine the composition of the bombs by sampling the air that circled the world.

The US Atomic Energy Commission collected information on the radioactive isotopes in human, animal, and plant tissues from around the world, in the secret project called "Project Sunshine," for the purpose of learning how many bombs could be exploded withot killing the entire world's population.

Thomas Edison, who had begun working with x-ray machines in 1895, became an opponent of their use after 1903, when one of his employees died of cancer that began in his hands and arms. By the 1930s, many people outside the medical profession were warning that diagnostic x-rays could cause accelerated aging, heart and circulatory disease, and birth defects, as well as causing cancer and leukemia. This public awareness of the danger of ionizing radiation was the reason that the government felt obliged to lie about the nature of the bombs and their effects on people and the environment. Many people, even in the US, were asking the government to stop the bomb tests, and to discuss nuclear disarmament. Two members of the US Congress (Senator Morse and Congressman Porter, both of Oregon) introduced bills in 1957 to stop the tests, but most congressmen, and President Eisenhower, believed that the US would be able to achieve a degree of technical advantage that would permit them to eliminate the Soviet Union in a first strike. This plan was closely involved with the need to study the effects of radioactive fallout on people and crops. The highest military officials were still pressing for a first strike in the 1960s (Douglas, 2008).

Science professors, including Linus Pauling, and some high school teachers tried to educate the public about the biological effects of radiation, but the US government mobilized effectively against them, for example by sending FBI agents

to make inquiries that implied that they were "disloyal citizens." Linus Pauling's passport was revoked because of his efforts to inform the public. At the same time, the Atomic Energy Agency and other branches of government, and the corporations that were involved in manufacturing bombs and nuclear power reactors, were employing experts to assure the public that ionizing radiation was absolutely harmless, below a certain level of intensity, the threshold at which harm would suddenly begin, and that below that dose, it could even be biologically beneficial.

John Gofman was one of the most visible of those government employees who argued that there was no basis for suspending atmospheric bomb tests. As the co-discoverer of protactinium-232, uranium-232, protactinium-233, and uranium-233, who later became a medical doctor, he was a favorite of the nuclear agencies for convincing the public that ionizing radiation was nothing to be feared.

In an interview several years ago, Gofman said "I was stupid in those days. In 1955, '56, people like Linus Pauling were saying that the bomb fallout would cause all this trouble. I thought, 'We're not sure. If you're not sure, don't stand in the way of progress.' I could not have thought anything more stupid in my life.

"The big moment in my life happened while I was giving a health lecture to nuclear engineers. In the middle of my talk it hit me! What the hell am I saying? If you don't know whether low doses are safe or not, going ahead is exactly wrong. At that moment, I changed my position entirely."

"There is no way I can justify my failure to help sound an alarm over these activities many years sooner than I did. I feel that at least several hundred scientists trained in the biomedical aspect of atomic energy--myself definitely included--are candidates for Nuremburg-type trials for crimes against humanity for our gross negligence and irresponsibility. Now that we know the hazard of low-dose radiation, the crime is not experimentation--it's murder."

Many ordinary people were making exactly that argument in the 1950s, but government censorship kept the most incriminating evidence from the public. The climate of intimidation spread throughout the culture, with large numbers of dissenters, especially between 1950 and 1965, losing their jobs in government, schools, universities, and industry. Now, the increasing numbers of people who don't want x-rays are still treated as crackpots.

Probably because of this continuing political-cultural situation, Gofman's recommendations in recent years have been very mild--simply for doctors to use good technology and to know what they are doing, which could lead to a ten-fold or even hundred-fold dose reduction in diagnostic x-rays. Even with such mild restraint in the use of diagnostic x-rays, Gofman's well founded estimate is that 250,000 deaths caused by radiation could be prevented annually. I believe many more deaths would be prevented if ultrasound and MRI were used consistently instead of x-rays. Using Gofman's estimate, I think we can blame at least ten million deaths on just the medical x-rays that have been used inappropriately because of the policies of the U.S. government in the last half century. That wouldn't include the deaths caused by radioactive fallout from bomb tests and leaks from nuclear power plants, or the vast numbers of people mentally impaired by all sorts of toxic radiation.

In the 1950s, many people believed that Gofman was just another government whore, like the other prominent scientists who supported atmospheric tests and argued against the "linear, no threshold" model of radiation damage. His description of a sudden recognition of the irrationality of his position is a powerful illustration of the way an authoritarian culture can affect the thought processes, but as far as I know Gofman never tried to explain his bizarre subservience to the social-political-economic power structure of US society. Most of his contemporaries failed to reconsider their actions and policies.

Some of the survivors from that period are continuing to pollute the discussion of the biological effects of radiation. Hired by the nuclear industry to present lectures to their staff, as well as to the public, they publish articles in books and magazines sponsored by the nuclear industry, and appear in advertisements for the industry.

For more than 50 years, the arguments of the pro-radiation factions have centered on a few situations, illustrations, and anecdotes that they know are effective propaganda, because each one consists of little more than a single image. These situations are predictably used to convince people that radiation exposure is harmless: A trip in an airliner, or living in Denver, exposes a person to hundreds of times more radiation than living near a nuclear reactor does; a sheet of ordinary paper stops a beam of radiation; living in homes with high radon levels prevents lung cancer; living in radioactive apartments in Taiwan prevented 96.5% of cancers; workers in the nuclear industry have a lower incidence of cancer than other workers.

These perennial arguments are now being used to sell radioactive rocks to cure cancer. The idea of "radiation hormesis," that a small amount of radiation is positively good for the health, is even being popularized by internet sites such as Dr. Mercola's.

To counter those propaganda images, the people who want to urge caution with ionizing radiation have discussed the processes that are known to occur when a certain type of radiation interacts with a certain type of substance, and have pointed out that, despite the large amount of knowledge that exists, the specificity of these interactions and the complexity of the living substance mean that science has only begun to understand the biological effects of radiation. While emphasizing the fragmentary nature of the science, a few of these people have spent years collecting the best information available on the health effects of radiation in a few well defined situations.

Ernest Sternglass is occasionally mentioned by the nuclear apologists, as a complete quack who hasn't done anything of value, and that he contradicts the authoritative conclusions of T. D. Luckey. Anyone who actually reads some of Sternglass's books and articles, and then examines Luckey's work, will understand the situation. Sternglass presents a large amount of very meaningful data, and he also describes the actions of government and industry officials who have made great efforts to hide dangerous information. Luckey repeatedly cites a few propaganda pieces as if they contained valid data, which they don't. And Luckey is apparently the best that the industry can offer.

When a physicist compares the radiation received from cosmic rays in Denver to the radiation from military or industrial nuclear fission products, implying that the "smaller dose" from artificial sources is less harmful "because it's much smaller," he is lying. A radioactive particle that decays in the body delivers most of its energy to the tissues, but external radiation of very high energy, such as cosmic rays, gamma rays, or very high voltage x-rays, delivers a smaller proportion of its energy to the tissues.

The person who demonstrates that a beam of "radiation" (which consists of alpha particles) can be stopped by a sheet of paper is illustrating the sort of thing that happens when fission occurs within the body. If an alpha particle is released inside the body, its energy will be absorbed in a very short distance, causing very great damage in a small region (Hei, et al., 1997).

People whose houses are chronically contaminated with increased levels of radon gas don't have an abnormally high incidence of lung cancer. But why would radon be expected to cause lung cancer? It's fat soluble, and it concentrates in fat tissues, bone marrow, and the brain and other nerves. Its concentration is about 10 times higher than normal in the brains of Alzheimer's and Parkinson's disease patients (Momcilovic & Lykken, 2007), and maps of the incidence of Alzheimer's disease in the US coincide with maps of radon emissions. People who talk about the negative association of lung cancer with radon exposure clearly aren't interested in learning the harmful effects of radon exposure.

The original article about the radioactive apartments in Taiwan, whose occupants had only 3.5% as many cases as would be expected from the rate in the general population, was written by W. L. Chen and 13 co-authors. Chen and at least 12 of his co-authors were closely associated with the nuclear industry or the military. The article gives no definite information about the distribution of the radiation within the apartments, about

the general health and mortality rate of the residents, or about the ages of the tenants. The article was published in the ***Journal of the Association of American Physicians and Surgeons.*** (This magazine was formerly named ***Medical Sentinel.)*** The ***New York Times*** described AAPS as an "ultra-right-wing . . . political-economic rather than a medical group," and most of the articles are advocating extreme economic and political action. Yet most of the people who argue that Chen's article is evidence of the harmlessness, or beneficial effects, of radiation, including T. D. Luckey, list it in their references, as if were a scientific report.

Even the mainstream professional journals haven't had a good record for objectivity. R. E. Alexander, a former chairman of the Health Physics Society's public relations committee, told the society's board of directors that Ernest Sternglass's work had led to publicity that was damaging to the nuclear industry. He said that the "basic publicity objective" of the Society was "to let the public know that due to a frankly acknowledged need, we have a new technology, health physics, which will permit them to enjoy the benefits of nuclear energy safely." Facts about the harmful effects of radiation were harmful to the Society, but "while we try to avoid publicizing papers that do not contribute to our basic objective, there is no way to prevent such publicity absolutely."

From my own experience, I think that kind of deference to economic interests is common in the major science journals in all fields.

Another journal that serves the industry is ***Radiation Protection Management.***

One of the current authors in ***RPM*** is Mark Hart, who mentions how he tries to prevent his audience from thinking "this guy must work for the government." He arranges to have himself introduced as a person who is displaying his personal collection of antiques (radioactive antiques), and that he has taken his vacation time to present the lecture.

"This demonstrated that I was not being paid by the Laboratory [Lawrence National Radiation Lab] to give the talk." "I make a point of separating the contents of my presentation from whatever the stance of my employer may be on this subject. I point out that the information that I will present is not my perspective nor the result of any research that I have conducted: I am only presenting a 'book report,' a very elaborate book report with examples on display that are integrated into the talk. I am presenting the very same information that the audience can read for themselves. To this end the presentation encompasses the range of authors from Gofman (linear hypothesis) to Luckey (hormesis) and ties historical experience to the common understanding of radiation and radioactivity." "We must also remember that credibility is lost if the audience is taken too far, too fast." "For instance, tell an audience that more people have died in the United States from airbags than died at the Chernobyl accident."

Hart's comment on the linear hypothesis: "This conservative approach was adopted assuming *any* amount of radiation would put a person at a quantifiable risk. There is little direct evidence of this, and there is disagreement about its veracity, even among radiation professionals." His use of the word "veracity" in relation to evidence implies that some professionals are lying about the evidence, but his context makes it clear that he is referring to people like Gofman.

In 1959, I suggested that my students, reading about the effects of radiation, should notice who the authors worked for. It was immediately obvious to them that government employees never mentioned that radiation could be harmful.

The people in the various professions who insist that "small" amounts of radiation are perfectly safe, or beneficial, seldom say much about the mechanisms involved in the harm or benefit of radiation. They suggest that the ionizing radiation stimulates mechanisms that repair damaged genes, when it damages them, or that it "stimulates the immune system." The very old idea, developed more than 80 years ago, that radiation's biological effect is produced exclusively by causing genetic damage, continues to be central to their thinking. This view dominates the thinking of dentists and physicians, as well as those in the business of "protecting public health."

At the beginning of the 20th century (e.g., H.J. Muller, 1910, 1921) when nothing was known about the physical or chemical nature of "the gene," many biologists committed themselves to the belief that "the gene is the basis of life."(Ann Rev of Genetics vol. 2:1-10, 1968, G. Pontecorvo, Hermann Joseph Muller; page 1). When it was discovered that x-rays produced mutations it seemed obvious that it was because they changed the "genes," and later when genes came to be identified with DNA, it was believed that radiation had its biological effects because of its effects on DNA, which continued to be thought of as "the basis of life."

The idea is that at the moment radiation is absorbed by a tissue, a DNA-gene is damaged, or not. Studies of DNA in isolation have contributed to some mistaken ideas about radiation safety; at one time the mere size of the DNA molecule was thought to determine an organism's sensitivity to radiation. In living cells, according to the older explanation, if the amount of DNA damage isn't too great, it will be repaired, and the radiation will have had no effect at all. A greater amount of DNA damage might be incorrectly repaired, producing a mutation, that could produce cancer, or, if the gonads were exposed to radiation, an inherited defect could be produced. Any damage would be instantaneous and local, and the repair would take place within minutes or hours, so by analyzing the DNA (usually just looking for structural changes in chromosomes), the degree of damage could be determined soon after the exposure.

This localized "genetic" explanation for the harmful effects of radiation was the predominant ideology of Anglo-American biology. William Bateson, who promoted the genetic doctrine of Gregor Mendel, and his followers such as Charles Davenport, wanted to deny absolutely the possibility that environmental influences could influence traits such as intelligence; each trait was determined by a gene. At the same time, 1902-1914, Theodor Boveri was explaining the formation of cancer by radiation or chemical carcinogens in terms of an induced imbalance of chromosomes, produced by changes in the process of cell division. The sorting of chromosomes during cell division became unstable under the influence of various harmful factors. Boveri saw that disturbing the chromosomes of an embryo could cause cells to stray out of their normal developmental path, and reasoned that this is similar to what happens in cancer--a disorganization of cellular interactions. But William Bateson didn't acknowledge that chromosomes carried genetic information until 1922, and his influence greatly retarded Anglo-American study of the biology of chromosomes, and of cancer.

This old idea (Boveri's) of genomic or chromosomal instability has become central to understanding the real effects of radiation on organisms. The fact that bacteria and other single-cell organisms contain DNA isn't enough to allow them to be considered as models for understanding the biological effects of radiation, because the existence of more complex organisms depends on the coordination of cells, based on signals and perception of wholes. The nature and the quality of our development depends on the degree of our cells' vigor and sensitivity in responding to, maintaining, and creating our long-range coherence. The sorting of chromosomes is one of the processes affected by the cells' basic vitality.

On the intracellular level, organization and sensitivity depend first on the interactions of water, electrons, and proteins, supported by the modifying effects of carbon dioxide, sugars, fats, nucleic acids, salts, and other substances. The crucial regulatory processes occur within a narrow range of energy changes. Interacting cells communicate their needs by excitatory signals that mobilize other parts of the system to make adaptations. Excitatory signals imposed arbitrarily from the outside on the adapting organism can create a state of arousal without a defined purpose, meaning that in the absence of a goal that can be achieved, the excited state may expend resources that could have been used productively in other ways.

Ionizing radiation is one source of such misleading excitatory signals, and even apart from its ionizing effects, it is likely to transmit enough extraneous excitation to the delicately balanced living state to change its organization and sensitivity.

When a man receives ionizing radiation to the head (Tamminga, et al., 2008), his sperms are destabilized in such a way that they are able to carry the instability with them into the fertilized ovum and the developing offspring, increasing the risk of developing leukemia.

Leonell Strong, who had studied genetics with T.H. Morgan and began breeding a strain of cancer-prone mice in 1921 for use in cancer and genetic research, gradually began thinking in terms of environmentally induced genetic instability. Excessive estrogen, and changes in the metabolism of the liver were the two factors that he focused on. He found that if a pregnant cancer-prone mouse received injections of a liver extract, several generations of the descendants would be free of cancer. The genetic instability that caused them to reliably develop mammary cancer was an inherited metabolic condition which could be corrected by a metabolic treatment.

It had been known for several decades that both estrogen and ionizing radiation produced cancer, when in 1971 Segaloff and Maxfield showed that they are synergistic. Irradiation produced cancer much more quickly when the rats had been treated with estrogen. In 1973, Segaloff treated 3 groups of rats, (1) with estrogen and radiation (800 R of X-rays to half of the body), or (2) with estrogen, radiation and progesterone, or (3) with just radiation and progesterone. As in the earlier experiment, many tumors quickly appeared on the side of the body that received the radiation in most of the animals of group 1, but in group 2 only one eighth as many tumors appeared in the animals that received progesterone. In the third group, no tumors appeared in the irradiated animals that received progesterone.-

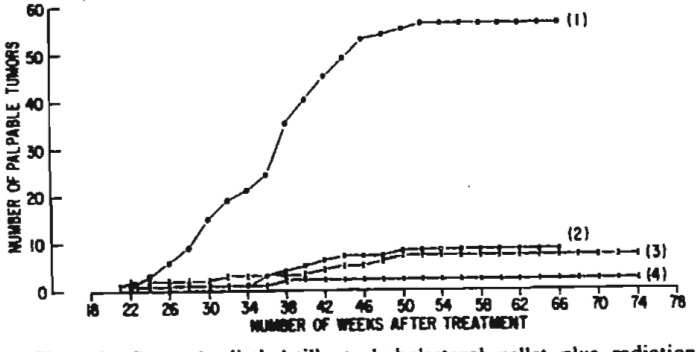

Chart 1. ***Curve 1***, **diethylstilbestrol-cholesterol pellet plus radiation (radiated side);** ***Curve 2***, **diethylstilbestrol-cholesterol pellet plus radiation (nonradiated side);** ***Curve 3***, **diethylstilbestrol-cholesterol pellet plus progesterone pellet plus radiation (radiated side);** ***Curve 4***, **diethylstilbestrol-cholesterol pellet plus progesterone pellet plus radiation (nonradiated side).**

This protective action of progesterone against radiation implies that X-rays have "estrogenic" effects on the body. This had previously been demonstrated very literally, when it was found that irradiating any part of the body of a female animal caused it to go into estrus, behaviorally as well as physiologically and biochemically.

Toxic heavy metals can also sensitize animals to radiation (and some metals, such as cadmium, have estrogenic effects). Stress of any sort tends to increase the formation of estrogen, and estrogen activates many mediators of inflammation.

Forty years ago, all carcinogens were dogmatically considered to be mutagens, but gradually the idea of "non-genotoxic carcinogenesis" has been recognized, along with the idea of genetic instability. Estrogen is typical of this type of carcinogen. Heat exposure, "serum starvation," and the tumor microenvironment are examples of non-genotoxic factors that can induce the instability (Li, et al., 2001). If the local environment of the tumor is carcinogenic, the tumor could grow by "induction" of defects in normal cells, rather than just by multiplication of its own cells. (I have proposed that carbon monoxide produced by a tumor could be a factor in the enlargement of the tumor, by induction of stress in surrounding cells.)

When destabilizing factors are transmitted from cells that were damaged, for example by irradiation, to other cells that weren't exposed to the radiation, but which then undergo changes similar to those of the exposed cells, these changes are called "bystander effects." Besides being transmitted from one part of the body to another, for example from the head to the reproductive organs, these effects can even be transmitted from one animal to another, for example from fish exposed to radiation to other fish which enter water after the exposed fish have been in it (Mothersill, et al., 2007). Serotonin has been identified as one of the substances transmitting the effect (Poon, et al., 2007). In some situations, the transmitted factors include nitric oxide and "persistent" free radicals (Harada, et al. 2008).

Besides transmitting the destabilizing effects through space, the effects can also be transmitted through time. Between 1988 and 1992, people

who survived the atomic bomb in Hiroshima in 1945 were tested for signs of inflammation, and their leukocyte counts, erythrocyte sedimentation rate, alpha-1 globulin, alpha-2 globulin, and sialic acid levels were increased in proportion to the amount of radiation they had been exposed to (Neriishi, et al., 2001). Twenty years after people were exposed to radiation by working at the reactor site after the accident at Chernobyl, their blood serum was compared to that of people who weren't exposed. Serum from the exposed workers caused chromosome damage and loss of viability in test cells (Marozik, et al., 2007).

G. Csaba's idea of hormonal imprinting is that a pattern is formed in the cytoplasm in response to the environment, and that this pattern can be passed from generation to generation if it is useful (Csaba, 1986). The persistent bystander and even transgenerational effects of radiation can be thought of as a kind of negative imprinting, a disruption of useful cytoplasmic patterning. The outcome of any cellular destabilization can be influenced by many things, even years or generations later. Even seemingly normal identical twins and cloned animals have recognizable differences, resulting from slight instabilities in the imprintable factors that regulate development (Dolinoy, et al., 2007; Weidman, et al., 2007; de Montera, et al., 2010; Wong, et al., 2010; Zwijnenburg, et al., 2010).

Prenatal or neonatal exposure to extremely small amounts of the estrogenic substances used in plastics, nonylphenol and bisphenol-A, have been found to greatly increase adult sensitivity to estrogen (Wadia, et al., 2007; Soto, et al., 2008). The synergy of estrogen and ionizing radiation suggests that early exposure to either could increase adult sensitivity to both.

The bystander effects include alterations in energy metabolism (Nugent, et al., 2010), movement, mitosis, and cellular orientation or perspective. Cells have different degrees of mobility, from muscle and bone cells to leukocytes, and the integrity of the organism depends on the appropriateness of their movements. Cells have to know where they are, and when, to coordinate their activities in space and time, knowing not only when to divide, but exactly how to orient the direction in which the division will occur.

Although I consider every cell to be a potential stem cell, it's helpful to consider the nature of the "stem cell function" in a general sense. The cells in the basal layer of the skin or intestine, for example, are well known stem cells. With each division, one daughter cell stays in place as a stem cell, while the other migrates toward the surface, as a differentiating and functioning replacement cell. (In the brain, cells migrate from a zone around the ventricles into the brain.) This is an asymmetric division, which must be oriented exactly, so that the basal layer continues to contain stem cells, rather than differentiated cells. The extracellular matrix surrounding the "stem" cells participates in the orientation of the asymmetrical division. Without proper orientation of the cell and its matrix, tissue renewal would fail.

In the 1920s and 1930s, when the idea of developmental fields guided many areas of research, numerous biologists considered that electrical and electromagnetic fields interacted with chemical processes, permitting cells to sensitively regulate their size, shape, orientation, and interactions with their surroundings. W.F. Koch, Alexander Gurvich, Albert Szent-Gyorgyi, and G.W. Crile did many experiments demonstrating the biological effects of electrons and photons, but in the spirit of reductionism corporate science bitterly rejected their work for several decades. A few groups have been bringing their ideas up to date, in ways that help to understand bystander effects, lingering inflammatory effects, imprinting, transgenerational effects, and that suggest new types of therapy.

Gurvich, and more recently many others including F.A. Popp, have demonstrated that normal cells emit weak photons in the visible and ultraviolet spectrum. Popp's laboratory has demonstrated that DNA can "store photons," by forming stable excited electronic states between nucleotide bases. Excited states in proteins can be transmitted to other proteins (Lardinois, et al., 2003), and the water close to proteins can maintain the excited states of electrons produced by oxygen over long periods of time (Marchettini,

et al., 2010; Voeikov, 2001, 2002, 2007; Voeikov & Malenkov, 1971, Voeikov, et al., 2003).

Enzymic reactions in normal metabolism can create a variety of excited electronic states which contribute to the store of photons and electrical fields. In plants, light creates an excited electronic state in chlorophyll, which is used metabolically, generating cellular fields similar to those in animals. The random processes of free radical oxidations in unstable lipids can also create excited states and photons, but they are distinct from those produced in normal metabolism. Deeply penetrating ionizing radiation is a unique source of random excitation of electrons, contributing to the burden of random stimulation.

In the normal metabolic oxidation and reduction, orderly electrical fields are generated, and the polarity of these fields is closely related to the alignment of the parts of the cell that regulate movement and cell division. When an external electrical field is applied experimentally, the centrosome, Golgi body, microtubules and other parts of the cell align themselves with the field, the cytoplasm streams, and the cells migrate toward the external cathode.

Injured cells behave like cathodes, producing the strongly negative "injury potential." Intensely stimulated cells produce a similar field, and it has been known for many years that brain cells will migrate toward an area of excitation. But disoriented cells don't migrate appropriately.

Since the normally oriented fields are maintained by metabolically excited electrons, and govern the quality of tissue renewal, the random electronic and light activity produced by lipid peroxidation and other toxic processes threaten the basic organization of the animal or plant. Vitamin C and the intrinsic "antioxidants" protect against these electronic disturbances, and can reverse some of the bystander effects produced by radiation and other stresses.

Even ultraviolet light can produce electronic excitation and bystander effects that destabilize cells, but, unlike gamma rays and x-rays, ultraviolet light doesn't penetrate deeply into the body. In visible light, it is only the red component that can pass deeply into the tissue, and it happens that red light is able to "quench" many excited electrons, restoring them to their normal resting or ground state. In a solid material, such as a seed or hair or bone, excited electrons will persist for a long time (hours in the seed and hair, years in bone), but with a brief exposure to red light, they will return to their normal state.

This beneficial effect of the red component of sunlight helps to keep plants from being sunburned. If the red light is removed from sunlight, even the blue light by itself is quickly toxic to their mitochondria. During the night, animals' respiratory enzymes lose some of their effectiveness, possibly from the effects of random lipid peroxidation, and red light restores their activity.

Heat stress and increased pH contribute to the generation of random electronic excitation, and light is protective in plants, partly by allowing carbon dioxide to be produced. In all cells, CO2 helps to control the general electronic state, lowering the pH and protecting the essential molecules from random excitations, oxidations, and reductions.

Under natural conditions, cosmic rays are an important source of random electrical excitations. At high altitude, their high energy causes them to have a low "linear energy transfer," LET, affecting tissues only slightly as they pass through, and at sea level the secondary and tertiary rays produced from the collisions of primary cosmic rays with the atmosphere have a higher LET, which is probably responsible for the lower mortality from cancer and heart disease at high altitude. But the lower oxygen pressure at high altitude, and greater retention of carbon dioxide in the tissues, would also reduce the tissue damage from radiation.

There are two species of bacteria that can withstand extremely large doses of ionizing radiation, and carbon dioxide seems to be the crucial factor in the ability of their proteins to function, even when their DNA has been fragmented by intense ionizing radiation.

The recognition of the coherence of the organism on the molecular and electronic level makes it clear why there can be no threshold of safety for ionizing radiation, but it also suggests new

approaches to preventing and treating the developmental and degenerative diseases.

Meanwhile, people in the US are being offered CAT scans to "detect early signs of heart disease" in a test that "takes only 20 to 30 minutes," and for other trivial reasons, with the approval of state radiation regulators, and without interference from the FDA. Hundreds of people recently experienced loss of hair in a stripe around their head after having x-ray scans, when their doctors intentionally used high doses to get clearer images. Paralysis and dementia are likely to follow in a few years, but few doctors recognized their bizarre hair loss as an indication of radiation poisoning. Many hospitals use low voltage x-rays for mammograms, with high LET and increased carcinogenicity, to get better images.

In California, where hundreds of the destructive head scans were done, tort reform law means that noneconomic damages for medical malpractice are limited to $250,000, from which a successful litigant would have to pay the lawyer. Premature death or dementia would be likely to precede any legal victory.

The culture that has made these bizarre medical radiation exposures possible is being sustained and expanded every time your dentist or physician explains the safety of "digital x-rays," or "dual photon bone scans," or mammograms.

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Ray Peat's Newsletter

For every thing that lives is holy, life delights in life. . . . *William Blake*

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Cancer: Disorder and Energy

According to the World Health Organization, cancer is now the leading cause of death in the world. Although many "causes" are known, and despite the "War on Cancer," nothing practical has been done to reduce the incidence of cancer. Since Nixon started that war, the number of people dying annually in the US has increased faster than the population. In ancient Rome and Egypt, cancer was rare; cancer has been identified in only one Egyptian mummy. In the US and several other countries, between 2002 and 2005 there was an unprecedented decline (7% in the US) in the incidence of breast cancer, when the medical use of estrogen decreased following the Women's Health Initiative report showing that estrogen caused cancer, dementia, strokes and heart attacks. However, when the public was reassured about estrogen's safety, breast cancer incidence began increasing again each year.

The cancer industry has been flexible and imaginative in ways of presenting "age standardized" death rates to show that they are making progress against cancer, but there are philosophical and scientific problems in "oncology" (i.e., the study or treatment of lumps) that should be considered by anyone who plans to do business with that profession.

In the 19th century (in Johannes Muller's lab), cancers, like other animal tissues, were found to be made up of cells, and by 1858, all diseases were said to be caused by disturbances in cells (Rudolph Virchow). The atomic and molecular theory of matter was becoming accepted at the time that animals were found to be made up of cells, and in both cases the "elementary particles" seemed to have a special power to explain things. This idea of a cellular basis of disease gradually displaced the old idea that diseases were caused by an imbalance of the body fluids, or humors. In 1863, Virchow recognized that inflammation, involving leukocytes, was a common feature of cancer, but that aspect of his work was neglected for a long time.

Recent medical textbooks reveal no major change in the understanding of cancer since Virchow's time, except that "genes" (which weren't known during Virchow's life) gradually became the most important aspect of cells. The typical modern textbook describes the cellular disturbance of cancer as the result of an "initiating" mutation in a gene, which gives it the potential to develop into a cancer, if it subsequently is exposed to a "promoter," which causes it to multiply. In some versions of the theory, a promoter is a second mutation that causes proliferation, but in other versions the promotion is caused by chemicals binding to receptors the way hormones do, to stimulate proliferation. Typically, textbooks (and reports of continuing research) describe subsequent changes in the genes that cause a cancer to progress from a simple excess of cells through stages of increasing malignancy: hyperplasia, dysplasia, carcinoma in situ, invasive cancer.

One of the reasons that the medical understanding of cancer hasn't changed significantly since Virchow's time is that blaming misbehaving cells for causing a tumor fits into the older medical tradition, that has existed at least since the time of Hippocrates, 400 BC, which treated tumors either by cutting them out, or by burning them off with caustics. Virchow's identification of misbehaving cells provided a clear mental image of exactly what the physician must try to destroy. And it's probably hard to get interested in

something which could seriously limit your professional activities if it turned out to be true.

The "cellular basis of cancer" was developed simultaneously with the germ theory of disease, and in the case of cancer, the deviant cells came to be considered an alien substance, "not-self," analogous to infective germs. Paul Ehrlich's search for poisons that were specific for bacterial pathogens was quickly extended to the idea of finding poisons that would distinguish between cancer cells and the patient's cells.

Hippocrates' therapeutic approach to cancer may have survived for 2400 years, but the ideas of his younger contemporary, Plato, about order and causation have probably had a greater effect on medicine. Plato believed that the world of experience is inferior and accidental, and that there are timeless "Forms" that are the real substances. In the atomic theory of matter, eternal, unchanging atoms took the place of platonic forms, and there are still molecular biologists who insist that life can only be explained in terms of its constituent atoms ("What else is there but atoms?"). This philosophy of timeless forms was a deep commitment of people like Gregor Mendel and August Weismann, whose ideas dominated the thinking of early 20th century geneticists. Genes were the immutable essence of organisms, and the cells, tissues, and organs that form the organism are merely temporal and accidental. Weismann's "germ plasm" or germ line contained the immortal genes, the rest of the body lacked them, and was essentially mortal.

For most of the 20th century, the official doctrine was that most of the cells of the adult body became stationary once the body reached its adult size, and that aging consisted of the "wearing out" of those mortal cells. When a tumor, containing new cells, would appear and grow, these cells were called "immortal," because they didn't follow the rule for normal, stationary, mortal cells. Their "immortality" is often demonstrated by growing them endlessly in culture dishes. Normal cells, if they can be made to survive in a culture dish, are likely to be "transformed" into cancer, demonstrated by their ability to replicate in dishes.

This is an important ideological point, that developed as biologists were experiencing the extreme difficulty of getting cells to replicate, or even to survive, in culture dishes. It has only recently been realized that cells need more than nutritional and hormonal signals to survive in culture; they require certain textural, structural, even rhythmically repeating conditions that mimic their surroundings in the living body.

Applied to cancer, the gene theory made it seem clear that the changes occurring in tumor cells were irrevocable, and it has seemed self-evident to oncologists that the only hope the cancer patient has is for the physician to destroy every bit of the alien substance. The recurrence of a cancer that has been removed has been evidence to them that fragments had remained, or that the cancer had distributed its seeds into other parts of the body. This seems to be the necessary conclusion if cancer is "caused" by defective genes.

New ideas of causality have grown up in science beside, or within, the science culture that is committed to platonism, reductionism, and genetic determinism. A few biologists, including Ana Soto and Carlos Sonnenschein, are applying more realistic ideas of causality to ecological, developmental, and cancer research. They have said (Soto, et al., 2009) "The ecological developmental biology (eco-devo) movement rejects the notion that development is merely the unfolding of a genetic program." If events such as cancer aren't "caused by genes," understanding the causes of cancer and the appropriate ways to treat it will require more holistic ways of looking at the tumor's relation to the organism, and the organism's relation to the environment.

It has been more than 40 years since experimenters demonstrated that cancer cells could be caused to revert to normal, by changing their environment. Harry Rubin (2006) has observed that cells can accumulate hundreds of mutations, and still function normally in the organism, but when separated and grown in a culture dish their differences become obvious. The surrounding cells in the body are causing the defective cells to remain normal in appearance, function, and growth behavior, instead of acting like cancer cells, and can also cause "stem-like" cells to

differentiate appropriately.. He says "Intimate contact between the interacting cells is required to induce these changes." When stem cells enter a tumor, they don't find that regulatory, normalizing interaction with normal cells.

Work like Rubin's shows that even "myriad" mutations don't necessarily cause cancer, and another line of research shows that things which don't cause mutations can cause cancer--the "non-mutagenic carcinogens." The presence of mutations is neither sufficient nor necessary for causing cancer, but tumors do eventually accumulate serious damage, which causes most of the tumor cells to die quickly. Biological stress, or excitoxic energy deprivation, destabilizes the genome; genetic changes develop as a result of prolonged destructive influences. The "non-genotoxic" carcinogens first cause inflammation, excitation, and energy impairment, leading to fibrosis, and atrophy. Cycles of cell injury, death, and repair cause chromosomes to deteriorate as the tissue loses its organization.

When a cell is stimulated, it responds, and the response requires energy. The stronger and more continuous the stimulus, the more energy the cell needs to continue responding. In some conditions, cells can desensitize themselves, to survive in the presence of continuous stimulation or irritation, but otherwise they are killed when they don't have enough energy to keep responding.

When a nerve is stimulated and responds, a wave of negative electrical charge passes through it; the electrical field accompanies a structural change in the cytoplasm of the nerve; similar changes occur in other types of cell. Stimulation of a nerve with negative (cathodal) polarity causes swelling, stimulation with the opposite polarity causes the opposite behavior; when nerve cells are inhibited, they shrink (Tasaki and Byrne, 1980; Tasaki, et al., 1988; Tasaki, 1999).

Swelling, an increase of the water content of an area of tissue, is a general feature of inflammation (Weiss, et al., 1951), whether it's in a lump caused by a bee sting, a bruise, or hives, or a cancer. Besides the instantaneous uptake of water described by Tasaki, there are increases that continue because of metabolic and chemical changes in the irritated cell. Tasaki has used gels of synthetic polymers to demonstrate that an electrical field can cause these changes, without the need for the "chemical osmotic" changes that are customarily assumed to account for the swelling changes caused by stress (Tasaki, 2002). When the pH of a protein gel becomes more alkaline, it swells. The electrical activation of a nerve causes a quick shift towards internal alkalinity (Endres, et al., 1986), followed by a sudden increase in lactic acid production. Although increased lactic acid causes acidity of an irritated or inflamed region, the conversion of pyruvic acid to lactic acid causes the interior of the stressed cell to become more alkaline, causing it to swell. This is the same process that causes the familiar swelling of tired muscles.

If blood vessels swell, the delivery of oxygen may be restricted, and hypoxia causes more intense swelling, because more lactic acid is produced, and less oxidized. This swelling pressure resembles an increase of osmolarity. For over 100 years, it has been customary to treat shock with "isotonic" fluids, which are in balance with well oxygenated tissues, with approximately 290 milliosmoles per liter, but this usually causes edema, swelling, and weight gain. Stressed tissues have been found to be in balance with fluids of much higher osmolarity, for example 372 mOsm/L (Tranum-Jensen, et al., 1981), and sometimes much higher.

Apart from its acidity, lactic acid acts as an excitatory signal. A very slight increase above the normal amount of lactic acid in the body fluids excites sensitive cells, and the amounts reached in inflamed tissues and in cancers will excite even stable cells such as myelinated nerves (Uchida and Murao, 1975).

Cancer cells show all the signs of being intensely stimulated, and this includes a high rate of oxygen consumption (deGroof, et al., 2009). The stimulation increases the energy requirements beyond the ability of the mitochondria's capacity to meet them, leading to the production of lactate even when a normal amount of oxygen is present. Even when both glucose and oxygen are supplied (which they usually aren't), the tumor cells will consume amino acids as fuel, as well as using them as material for growth. Tumors have been

called "nitrogen traps" or "glutamine traps," but this has meaning beyond the use of the nitrogen for growth; it is involved in the energetic inefficiency of this process, and the reorganizing effects this wasteful flow of energy has on the tissue structure (Medina, 2001). When glutamine enters the Krebs cycle to be used as fuel, this interferes with the ability to oxidize glucose, causing more lactic acid to be formed, contributing to the excitation and increased energy requirement.

Lactic acid activates the other major mediators of inflammation, including prostaglandins (made from PUFA), free fatty acids (including arachidonate, that forms prostaglandins; Schoonderwoerd, et al., 1989), nitric oxide, carbon monoxide, proteolytic enzymes that degrade the extracellular matrix, TNF (Jensen, et al., 1990), hypoxia inducible factor (Lu, et al., 2002; McFate, et al., 2008), interferon, and interleukins. Arachidonic acid itself can increase lactate production (Meroni, et al., 2003). TNFalpha and interferon gamma activate lactic acid production by increasing prostaglandins (Taylor, et al., 1992).

Most of the present information about cancer cells' behavior, such as reactions to radiation and chemical toxins, has been based on the study of cells in culture dishes. For more than 70 years, it was generally believed that radiation caused mutations and cancer by directly modifying the cells' genetic material. Then, it was discovered that fresh cells that were added to a dish of irradiated cells also developed mutations. The radiation causes cells to emit excitatory, inflammatory, substances such as serotonin and nitric oxide, which injure the cells that are later put near them.

Applying this information to the existing knowledge that radiation induces cancer in animals, the doctrine of genetic determinism inferred that the radiation "bystander effect" is just another mechanism by which radiation produces the "mutant cancer cell" or clone of cancer cells. But the difference between events *in vitro* and *in vivo* is that cells which are injured in the organism immediately initiate a process of healing, and in that situation each of the substances emitted by injured cells is acting both locally and systemically to activate repair or regeneration of the damaged tissue. Cells isolated in a culture dish can't call on the organism for the necessary materials, so the responses of the "bystander" cells, leading to mutations and death, seem meaningless. The injured cells are merely toxic, rather than potentially being a stimulus to healing.

When any part of a living organism is injured, for example by x-rays or surgery, the emitted substances affect the endocrine and nervous systems, activating processes that change metabolism and behavior. The injured tissue takes on new functions, for example by locally synthesizing estrogen, cortisol (Vukelic, et al., 2011), and other hormones, as well as stimulating the normal endocrine glands to secrete them. These interactions have been generally disregarded in cancer treatment, because of the gene-centered theory of cancer, but they are essential for understanding the "malignancy" of tumors, that property that makes them likely to return after the tumor has been destroyed, and to spread to other tissues. Has anyone ever heard of a radiologist or surgeon who measured estrogen or the various mediators of inflammation before, during, and after their treatments? Long range survival after breast cancer surgery is affected by the time in the menstrual cycle when the surgery is done (Lemon, et al., 1996).

All sorts of stress, inflammation, and tissue injury increase the concentration of estrogen, both locally and systemically. Estrogen in turn produces hypoxia, swelling, lactic acid formation, and stimulates cell multiplication. Even a brief period of hypoxia will cause the secretion of lactate and other chemoattractants (Neumann, et al., 1993), which will cause cells to move into the hypoxic area from the blood stream. Although lactic acid attracts immune cells, it probably reduces their anticancer functions, and it stimulates the formation of new blood vessels, supporting continued growth and expansion of the multiplying cells (Hirschhaeuer, et al., 2011). When a tissue is being repaired normally, the new cells sense a quorum, and stop multiplying. The return of nerves to the damaged area is part of the regenerative process; nerves have inductive and stabilizing effects on differentiating cells.

These complex interactions between tumor cells and the rest of the organism are not

considered by the ideology of medical oncologists. The ruling belief is that the malignancy of cells can be determined by examining them microscopically, and that their rate of growth can be determined, and that the tumor's approximate time of origin can be estimated. After surgically removing a tumor, the administration of chemotherapy and/or radiation is governed by mathematical descriptions of the expected behavior of cancer cells.

The mathematical relation of mortality to aging was described by Benjamin Gompertz, an actuary, in 1825, based on the understanding that people become less able to resist dying as they get older. This Gompertzian growth curve, which is realistic when applied to a population of people, flies, or rabbits, was applied to tumor growth (A.K. Laird, in 1964). Gompertz' reasoning that the probability of a person's dying increases with age has nothing to do with cancer cells, and there is very little evidence that his law of growth is useful for describing tumors. Laird's evidence consisted of 19 tumor samples, taken from 10 mice, 8 rats, and a rabbit. Her suggestion that the continuing deceleration of the growth rate might represent a natural growth regulating process wasn't influential, but her use of an actuarial formula, suggesting certain properties of cancer cells, has been extremely influential. It seems to be the profession's great need for justification that has made a Law of Tumor Growth so important to them.

At the time Laird did the tumor growth study, there was considerable interest in the idea that the immune system could be induced to prevent tumor growth. In 1951, Chester Southam, of the Sloan-Kettering Institute, tested his theory of cancer immunity on hundreds of patients and prisoners, and his results were widely reported. He found that pieces of tumor implanted in healthy people caused a local intense inflammation, which healed completely after two or three weeks. In sick people, the rejection of the cancer implant took about twice as long, and in people who already had cancer, the implant was very slow to be destroyed, and sometimes it was still present when they died.

In 1889, Stephen Paget had noticed that cancers metastasize only into certain organs, and compared the cancer cells to seeds that "can only live and grow if they fall on congenial soil." While many people, like Southam, saw a failing "immune system" as part of the congenial soil, and suggested vaccination to activate an immune rejection of the tumor, others have suggested "reducing the soil to dust," making growth impossible in a more general way. Recently, this attitude has taken the form of different ways of "starving" cancer, by reducing sugar in the diet, or by blocking cells' ability to use sugar. The idea of making the "soil" inhospitable to cancer is a variation on the theme of killing the unwanted tissue.

As long as the lump is defined as an alien material, killing it by any means seems reasonable, but if it is seen as the body's attempt to repair itself, then killing it is no more reasonable than it would be to cut the spots out of someone with smallpox.

When a cell is dying, it emits growth stimulating signals (Huang, et al., 2011). That's a normal part of tissue renewal. Some of its substance guides the differentiation of new cells, as demonstrated long ago by Polezhaev (discussed in my previous article, "Stem cells, cell culture, and culture: Issues in regeneration"). Anything that injures a tissue enough to require cells to be replaced causes the activation of a regulatory protein, hypoxia-inducible factor, HIF, which inhibits mitochondrial respiration, causing a shift toward glycolytic metabolism, increasing substances needed for growth. HIF is essential to the healing of any wound. Even glucose deprivation can cause the induction of HIF. Prostaglandins, made from polyunsaturated fatty acids released by stimulation, can cause HIF to increase, but HIF also causes prostaglandins to increase. Lactic acid increases the expression of HIF, while HIF causes cells to shift metabolically to depend on converting glucose to lactic acid, that is, to adopt the "cancer metabolism." HIF is recognized as a fundamental problem in "cancer therapy," since HIF allows the cancer to resist the treatment, but the treatment increases HIF.

Radiation, chemotherapy, and surgery all activate these processes of cell replacement, and

unless something has changed to improve the organism's recuperative ability, it isn't clear why the cells which replace the missing part should be more able to satisfactorily complete the recovery process than the original cells were. Even the amount of radiation in a single dental x-ray is enough to activate the excitatory-inflammatory processes, and a "therapeutic" x-ray to any part of the body excites similar, but much greater, processes throughout the body. But the ideology of "the cancer cell," and the Gompertz Growth Law, guide the practice of cancer treatment.

Many years ago, Harry Rubin was impressed by hearing from a pathologist that he had been able to find diagnosable cancer somewhere in the body of every person over the age of 50 that he had autopsied. If everyone has cancer by the age of 50, that means that cancer is harmless for most people, and that small cancers might frequently appear, and be spontaneously removed as part of the body's regular house-cleaning. One of the reasons that spontaneous regression of tumors seems so rare is undoubtedly that most tumors are quickly cut out by surgeons.

Preventing injury should be a basic consideration, but the medical slogan, "first do no harm," just doesn't apply to the cancer treatment industry, and this results from the doctrine of "the cancer cell," which is something to be destroyed or kept from multiplying. In the process of diagnosing a cancer, and during the course of treating it, the patient is usually subjected to multiple x-ray examinations, sometimes given radioactive drugs that supposedly concentrate in hidden tumors to emit positrons, and often has toxic contrast agents injected even for MRI examinations. These procedures, even before the destructive "therapies" begin, are adding to the body's inflammatory burden, interfering with the body's ability to complete a healing process. Decisions about pain control usually disregard the effects of the drugs on tumor growth and general vitality--for example, the opiates stimulate histamine release, which increases inflammation and tumor growth.

In 1927, Bernstein and Elias found that rats eating a fat free diet had almost no spontaneous cancer, and many studies since then in animals and people have shown a close association between polyunsaturated fatty acids and cancer. The polyunsaturated fatty acids in themselves, and their breakdown products, are excitatory and destabilizing to normal cells, but by modifying the sensitivity and energy production of cells, they limit cells' ability to respond to stimulation and destabilizing influences. Although they aren't essential for wound healing (Porras-Reyes, et al., 1992), they and their metabolites, the prostaglandins, are very conspicuous in wounds and tumors, and their proportion generally increases with aging. The prostaglandins are involved in several vicious cycles, including that with HIF mentioned above. This makes the PUFA and prostaglandins important to consider in relation to optimizing wound healing, and decreasing cancerization. Aspirin's protective and therapeutic effects in cancer are starting to be recognized, but there are several other things that can synergize with aspirin to reduce the circulation of free fatty acids and their conversion to prostaglandins. Niacinamide, progesterone, sugar, carbon dioxide, and red light protect against both free fatty acids and prostaglandins.

Since excitation leads to intracellular alkalinity and swelling, reducing the excitation seems reasonable, and many things which protect cells against excitation also have demonstrated anticancer effects. Local anesthetics, antihistamines, and anti-inflammatory substances and some anesthetics such as xenon (Weigt, et al., 2009) are safe. Inhibitory substances related to GABA are being investigated for their ability to stop tumor growth. Simply stopping excessive excitation tends to restore the dominance of oxidative respiration over glycolysis.

To restore the supply of oxygen, sugar, and nutrients, swelling must be stopped. Hyperosmotic fluids act directly on swollen cells, removing water. Stopping excitation allows a return to efficient metabolism and reduces the injury potential, allowing the pH to decrease; with lower pH, the cell releases some of its water.

Increasing carbon dioxide lowers the intracellular pH, as well as inhibiting lactic acid formation, and restoring the oxidation of glucose increases CO2. Inhibiting carbonic anhydrase, to allow more CO2 to stay in the cell, contributes to

intracellular acidification, and by systemically increasing carbon dioxide this inhibition has a broad range of protective anti-excitatory effects. The drug industry is now looking for chemicals that will specifically inhibit the carbonic anhydrase enzymes that are active in tumors. Existing carbonic anhydrase inhibitors, such as acetazolamide, will inhibit those enzymes, without harming other tissues. Aspirin has some effect as an inhibitor of carbonic anhydrase (Bayram, et al., 2008). Since histamine, serotonin (Vullo, et al., 2007), and estrogen (Barnett, et al., 2008; Garg, 1975) are carbonic anhydrase activators, their antagonists would help to acidify the hypoxic cells. Testosterone (Suzuki, et al., 1996) and progesterone are estrogen antagonists that inhibit carbonic anhydrase.

With aging, cells have less ability to produce energy, and are often more easily stimulated. The accumulation of polyunsaturated fats is one of the factors that reduce the ability of mitochondria to produce energy (Zhang, et al., 2006, 2009; Yazbeck, et al., 1989). Increased estrogen exposure, decreased thyroid hormone, an increased ratio of iron to copper, and lack of light, are other factors that impair the cytochrome oxidase enzyme.

The increased intracellular alkalinity and intracellular calcium that result from the combination of those factors increase the tendency of cells to be overstimulated, leading to aerobic glycolysis, the cancer metabolism. Improving any part of the system tends to increase carbon dioxide and decrease lactate, permitting differentiated functioning.

There are many people currently recommending fish oil (or other highly unsaturated oils) for preventing or treating cancer, and it has become almost as common to recommend a sugar free diet, "because sugar feeds cancer." This is often, incorrectly, said to be the meaning of Warburg's demonstration that cancer cells have a respiratory defect that causes them to produce lactic acid from glucose even in the presence of oxygen. Cancer cells use glucose and the amino acid glutamine primarily for synthetic purposes, and use fats as their energy source; the growth stimulating effect of the "essential fatty acids" (Sueyoshi and Nagao, 1962a; Holley, et al., 1974) shows that depriving a tumor of those fats retards its growth. The great energetic inefficiency of the cancer metabolism, which causes it to produce a large amount of heat and to cause systemic stress, failure of immunity, and weight loss, is because it synthesizes fat from glucose and amino acids, and then oxidizes the fat as if it were diabetic.

Estrogen, which is responsible for the fact that women burn fatty acids more easily than men, is centrally involved in this metabolic inefficiency. When a tissue is exposed to estrogen, within minutes it takes up water, and begins to synthesize fat, with a tendency to produce lactic acid at the same time. The alkalizing effect of lactic acid production is apparently what accounts for the uptake of water. Since it takes longer, at least 30 minutes, to produce a significant amount of new enzymes, these early changes are explained by the activation of existing enzymes by estrogen.

The transhydrogenases, or the transhydrogenase function of the steroid dehydrogenases, which shift metabolic energy between glycolytic and oxidative systems, have been shown to explain these effects of estrogen, but the transhydrogenases can be activated by many stressors. The biological function of the transhydrogenases seems to be to allow cells to continue growth and repair processes in a hypoxic environment. Estrogen can start the process by creating new pathways for electrons, and will promote processes that are started by something else, and progesterone is estrogen's natural antagonist, terminating the process.

Recently, a group at Johns Hopkins University (Le, et al., 2012) has been working out the implications of this ability to change the metabolism under hypoxia: Using an isotope-labeled amino acid, ". . . glutamine import and metabolism through the TCA cycle persisted under hypoxia, and glutamine contributed significantly to citrate carbons. **Under glucose deprivation, glutamine-derived fumarate, malate, and citrate were significantly increased.**" The implication of this is that if the tumor isn't supplied with sugar, it will increase the rate at which it consumes the host's proteins. Forty years ago the work of Shapot and Blinov was showing the same effect, except that

they demonstrated the involvement of the whole organism, especially the liver, in interaction with the tumor (Blinov and Shapot, 1975).

The alkaline cancer cell surrounds itself by the acid that it emits, and this extracellular acidity increases the ability of fatty acids to enter the cell (Spector, 1969); cancer cells, although they are synthesizing fat, also avidly take it up from their environment (Sueyoshi and Nagao, 1962b). This fat avidity is so extreme that cancer cells *in vitro* will eat enough polyunsaturated fat to kill themselves. This has been offered as proof that fish oil kills cancer. Saturated fats, however, have a calming effect on cancer cells, inhibiting their aerobic glycolysis (Marchut, et al., 1986) while permitting them to resume the respiratory production of energy.

The foods that nourish the patient well enough to support healing while permitting energy reserves to be built up are also the foods that don't interfere with the hormones, that don't cause spurious excitation of the tissues. The polyunsaturated fats directly stimulate the stress hormones, activate the excitatory amino acid signals, and directly excite cells, while the saturated fats have opposite effects, and are anti-inflammatory, and also don't interfere with mitochondrial function. When we eat more carbohydrate than can be oxidized, some of it will be turned into saturated fats and omega-9 fats, and these will support mitochondrial energy production. Carbohydrates in the diet also help to decrease the mobilization of fatty acids from storage; niacinamide and aspirin support that effect. Sugars are probably more favorable than starches for the immune system (Harris, et al., 1999), and failure of the immune system is a common feature of cancer. Polyunsaturated fats are generally known to suppress the immune system. Foods that provide generous amounts of sodium, calcium, magnesium, and potassium help to minimize stress. Trace minerals and vitamins are important, but can be harmful if used excessively--iron excess is important to avoid.

Emodin, an anti-inflammatory substance found in cascara sagrada bark and other plants, is similar to other molecules that have been used for treating cancer, and one of its effects is to lower HIF: "Consistently, emodin attenuated the expression of cyclooxygenase 2 (COX-2), VEGF, hypoxia inducible factor 1 alpha (HIF-1alpha), MMP-1 and MMP-13 at mRNA level in IL-1beta and LPS-treated synoviocytes under hypoxia" (Ha, et al., 2011). MMP-1 and MMP-13 are collagenase enzymes involved in metastasis.

When cells are fully nourished, supplied with protective hormones, and properly illuminated, their ability to communicate should be able to govern their movements, preventing--and possibly reversing--metastatic migration.

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Ray Peat's Newsletter

Medical genetics and immunology: Islands of fantasy in a sea of ignorance

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Implications of inflammation

It has become widely accepted that inflammation has a central role in several major diseases--atherosclerosis, cancer, Alzheimer's disease, diabetes and obesity, Parkinson's and Huntington's disease, asthma, epilepsy, for example--so understanding the nature of inflammation has gained special importance. For thousands of years, inflammation has been defined by the presence of swelling, redness, increased heat, and pain.

Is the inflammation the main cause of the disease, or is it instead, a response to the disease process? Not long ago, the medical profession began to see inflammation as an important part of the healing process, reflecting the actions of both an innate immunity and a learned immunity, and before that, it was seen, like fever, as the problem to be relieved, with "allopathic" treatments.

Soon after good microscopes were developed, Rudolf Virchow described the collection of white blood cells in infected areas and tumors, and suggested that their accumulation was a consequence of the damage to blood vessels and congestion, caused by tissue damage. They were incidental to the inflammation. A generation later, Elie Mechnikoff, who had studied the orderly and meaningful movements of cells in the developing embryos of a great variety of organisms, saw that the collection of white cells around a foreign material was intentional; in the case of the embryos of starfish, the white cells were part of the organism's digestive system. When he introduced rose thorns into the tissues of water fleas, the wandering cells engulfed and dissolved them. He reasoned that the pus that surrounds a thorn in a person's finger represents the same process--a protective eating and destruction of the harmful material.

For the Greeks and Romans, the pus of an abscess was "laudable," but by Mechnikov's time, pus had become identified with the presence of infectious microorganisms. Disinfectants were used to prevent the infections that could produce pus. However, by the end of the 19th century, sterile extracts of microorganisms were found to be able to produce the inflammatory signs of infection. Virchow's observation of white blood cells in cancers could be considered as an early recognition of sterile inflammation, but the term came into use later, and has appeared intermittently in the literature for many years. The concept has become more important as researchers have explored the interactions between the supposedly primitive, non-specific "innate immunity," and the supposedly more highly evolved specific adaptive immunity.

Trauma, prolonged interruption of blood supply, chemical injury, radiation injury, and signals from nerves are among the things that can cause sterile inflammation.

Although the concept of sterile inflammation has been in the medical literature for a long time, the influence of the drug industry has helped to keep it from entering significantly into medical education. In 1976, I was talking to a recent graduate of Stanford's medical school, and when I mentioned sterile inflammation, she interrupted, saying "there's no such thing, inflammation means that there's an infection." When the involvement of inflammation in neurological disease or atherosclerosis is mentioned, most physicians probably infer that this is evidence of a hidden infection or a mysterious new organism. It could be, but to assume that is to neglect the many other possible causes.

Mechnikov's idea of intentionality, goal directed behavior, in the wandering cells was antagonistic to the most powerful trend in science,

the doctrine of randomness in a mechanistic, deterministic view of matter. Following Descartes, the mechanistic materialists saw living organisms as machines, in which each part interacts mechanically with adjoining parts, and consciousness was something essentially distinct from the living substance of the organism. But as early as the 18th century, some researchers were thinking of the brain as an integrating center, not only for perception and movement, emotion and thought, but even for sickness and health.

The mechanistic materialists labeled such holistic thinking as anthropomorphizing or vitalism. Explanations were considered to lack "objectivity" if they related to a purpose; students were taught to avoid "teleological" explanations, if they wanted to be real scientists. However, from the time of Pasteur and the adoption of mass vaccination, the body's reactions to alien material were concretized in the concept of an "immune system," which existed for the purpose of defending against infections. It's important to remember what scientific knowledge about the nature of life was at that time—almost nothing that people believed at that time about how our bodies come into being, how they produce chemical changes, or how they move and sense, is now recognized as true. But the basic idea of an "immune system" has hardly changed in 100 years.

Although Mechnikov shared the 1908 Nobel Prize with Paul Ehrlich, Ehrlich's Nobel lecture expressed an extremely reductionist view of the organism, almost comical when juxtaposed to Mechnikov's lecture. According to Ehrlich, it was necessary for science to differentiate "the concept of the cell into that of a great number of separate, individual functions." In that lecture he talked about lock-and-key interactions, and receptors on cells. This was the course taken by science in the following century.

Mechnikov's goal directed phagocytes were accepted as part of the immune system that increasingly focused on Ehrlich's highly specific antigens and antibodies. Although the immune system was understood to have the purpose of defending the organism by destroying germs, it was put into an "objective" reductionist mechanistic scheme by giving it its own evolutionary explanation, through the natural selection of random changes in genes which, through time, became a very complicated machine that happened to kill germs, by strictly local molecular interactions. The germ killing, antibody forming immune system was thought to have evolved bit by bit, along with the evolution of the complex nervous, reproductive, and digestive structures and functions that distinguish mammals and people from sponges and roundworms, each feature the result of random changes that were preserved by natural selection.

By the 1960s, because of the ability through "vaccination" to create antibodies that would bind even to newly synthesized substances, the earlier idea of a simply genetically programmed immune system had to be abandoned, because the number of possible antibodies would have required a tremendous amount of DNA, that wouldn't fit inside a cell. New genetic explanations were invented to explain the ability of the immune system to adapt flexibly to unexpected new diseases. This was achieved by the idea of the immune system as a microcosm of evolutionary history, in which hypermutable genes could in a very short time evolve the new sequences needed to produce novel antibodies to destroy novel pathogens. It was still random, but very fast, and the cells that were selected, and stimulated to multiply, formed a clone, the way a mutant cancer cell formed a clone, supposedly giving each tumor its unique genetic individuality.

In an international immunology symposium at the University of Oregon in 1969, a few famous immunologists presented their recently developed theory about immunity, based on the neodarwinian theory of evolution as the result of random changes that are preserved by natural selection. The day after a description, to a large audience, of an experiment demonstrating clonal selection, in which specific immune cell clones were killed in a culture dish, and shown to stay dead, while other clones survived, an assistant professor of developmental biology described, to a small group of students, an experiment in which he had replicated that demonstration of clonal selection, and then repeated the same conditions, but with different concentrations of cells in the dish. With a sparse

cell population in the dish, his results were the same as those described in the earlier lecture, but when he increased the cell population to a certain point, the missing "clones" reappeared.

In the absence of a whole organism, but with a quorum of their peers, the cells were able to reconstitute a full repertoire of sensitivity. My impression as he described the experiment was that it implied that each cell had to have a knowledge of the type of organism it belonged to, rather than just being committed to expressing certain genes for the rest of its life. A few weeks later I met the professor in the hall and asked if he was publishing the experiment, and he said he hadn't written it up yet. I watched for it in the next few years, but never saw anything by him that related to it. Ten years later, a few other people began questioning the clonal deletion theory of self tolerance, but the many changes that have been made subsequently have been essentially to preserve the mechanistic randomness of the theory, and the doctrine that it is a system specifically evolved for fighting microbes. The goal-directedness introduced by Mechnikov was kept for the system as a whole, but the intentionality was reduced to random changes.

This doctrine of a separately evolved, and evolving, immune system provided no insight into the phenomenon of sterile inflammation, and it's that kind of inflammation, which lacks intelligible goal-directedness, that has become so important for understanding the chronic and degenerative diseases, and aging.

Before someone thinks of a mechanistic-neodarwinist theory of sterile inflammation, I want to propose a very different approach. Life is very adaptable, but it isn't infinitely adaptable. Life, in its highly complex forms, whether mollusk, mammal, fungus, or phanerogam, has many common features, and each type has a range of environments that are more or less suitable. The neodarwinian ideology inclines many biologists to assume that an organism's present form represents its best adaptation to its present environment, or to its recent past environments. This leads to arguments that "we evolved to eat ...," or to live in certain ways. But experiments in which animals become more intelligent and live longer when they are put into an environment which never existed in nature imply that organisms have their own internal principles that allow them to become more than they or their ancestors ever were, if they have the right environment.

The intrauterine environment permits injuries to be repaired, mostly without inflammation or scarring, and when some of those features, such as high carbon dioxide and sugar content are provided postnatally, inflammation and scarring can be prevented or reduced.

When prenatal environments are modified, the development of the animal's brain and metabolism is affected, affecting the course of that animal's life, and influencing subsequent generations. The wrong balance of prenatal nutrients can decrease the metabolic rate and increase obesity, or a better balance can increase brain development and alertness. When a young animal's early life is enriched with stimulation and opportunity for exploration, its brain development is improved (increased cortical thickness and enzyme activity), and those changes are passed on to subsequent generations, with cumulative effects if the improved environment continues to be available.

The prenatal absence of inflammation corresponds to conditions that are providing energy and other conditions necessary for a very high rate of metabolism, with minimal stress. Generalizing from an understanding of gestation, we could say that inflammation, and the failure of tissue maintenance, occurring later in life is the result of a gap between the energy that's available and the demands that are made on the organism or on a particular tissue.

This approach to understanding inflammation suggests why it contributes to degenerative processes, and suggests potential remedies, but it also offers a new perspective on the processes that are called innate and acquired immunity. The boundaries of what used to be called an immune system have been expanding and becoming blurred, as the interactions of nerves, hormones, nutrition, tissue repair, reticulo-endothelial system, phagocytosis, and wandering or stem cells come to be understood in more detail.

Jamie Cunliffe and Polly Matzinger have been developing a new understanding of the immune

system, centered on the idea that tissue damage is the main issue, rather than the distinction between self and nonself antigens. They recognize that the old model, especially the "adaptive immune system," is failing to explain things, and they are giving more weight to things such as inflammation that had been attributed to an "innate immune system," but what they are describing might better be described as an alert, intelligent organism maintaining itself.

This new orientation would make "stem cells" part of the "immune system," since they sense danger or tissue damage, and adapt to repair it. The wandering white blood cells, rather than being the end product of a particular clone, are able to transform themselves when they find themselves in new situations, becoming a different kind of cell. The signals that cause them to go where they are needed are related to inflammation, but this is exactly where immunology and stem cell research need to direct their attention. These signals are strongly influenced by environmental conditions.

One of the important features of the intrauterine environment is that it is steadily very warm, and that means that the fats which are synthesized from sugar will be relatively saturated. If sugar is deficient, which is common as a result of maternal hypoglycemia in the third trimester of pregnancy, free fatty acids from the mother's tissues and her diet will provide energy for the fetus.

The brain requires a high level of sugar for optimal growth, so maternal undernutrition or hypoglycemia will increase the ratio of the baby's body weight to its brain weight, and will change various other features of metabolism and structure. If the mother's fats are highly unsaturated, they can be turned into the pro-inflammatory prostaglandins during stress, and hypoglycemia during the third trimester is highly stressful for the fetus. Besides causing injury to the fetus during this time, producing inflammation and potentially scarring and granuloma or fibroma formation, the prostaglandins activate the stress hormones, such as corticotropin release hormone, which is a trigger for stimulating the birth process, and so tend to cause premature delivery.

These polyunsaturated fats, which are clearly alien to the gestational process, interfering in so many ways with optimal development, are present in the mother's tissues and foods because of the type of environment she occupies. If she ate only foods from a warm climate, where plants and animals produce mostly saturated fats, the fetus wouldn't be subjected to the anti-regenerative, pro-inflammatory, anti-developmental effects of the fatty acids and prostaglandins. The polyunsaturated fatty acids, prostaglandins, and inflammation, clearly encroach on the process of gestation, altering the subsequent life of the exposed individuals, causing them to adapt to the world by metabolizing less energy; they continue to constrain development throughout the lives of those who continue to be exposed to them.

The figures for premature births and low birth weight in recent decades suggest the importance of the issue. While adults are getting fatter, more underweight babies are being born. In affluent countries, while the adults' body size has increased during this time, their head circumferences haven't. These changes are similar to those seen in animals fed increased amounts of polyunsaturated fats. Besides being the precursors for the prostaglandins, the polyunsaturated fatty acids amplify inflammation and stress in a variety of other ways.

The prostaglandins are, in adults as they are in the fetus, central to the scarring, fibrosis, and failure of regeneration that are considered to be normal for mammals when they are injured or are aging. The failure of regeneration in a phylum of animals is closely related to their susceptibility to forming tumors. Cancer can be considered as a form of dystrophy, a consequence of tissue atrophy, a failure to keep regenerating. An example of this antagonism would be the experiment in which parts were cut off salamanders, allowing them to grow a new tail or leg, but when a tumor was grafted on where a tail was amputated, the tumor was converted into a tail, by the animal's "regenerative environment."

Before the recognition that adult tissues all contain stem cells, most biologists thought of the organism as being made up of "adult cells," that would last for a large part of a normal life span. Tissues were examined microscopically after they had been killed and hardened chemically, and it didn't occur to most researchers to think of the

image under the microscope as a single frame from a moving picture. G. Zaijecek has done experiments that reveal "cell streaming" in tissues normally thought of as static, such as the liver, pancreas, or the cornea of the eye. It has been recognized for a long time that when the cells of the adrenal cortex are regenerating they "stream" away from the outer capsule, changing their form and function as they go. Zajicek has showed evidence that a similar transformation of function occurs in the pancreas, with acinar cells turning into islet cells as they migrate (Zajicek, et al., 1990).

The innervation of some regenerating epithelial tissues, such as the bladder, skin, and cornea, has been studied in considerable detail, and it's fairly well known that the sensory nerves have complex "trophic" or sustaining effects in these tissue. For example, if sensory nerves are destroyed in an area of the skin, that area becomes thin and shiny. Since some of Pavlov's earliest studies, nerves have been known to have a trophic function on the tissues they innervate. In some tissues–bladder, stomach, heart, liver–complex chemical signals are known to be released by the sensory nerves, but the presence of nerves in other tissues, such as the cortex of the adrenal gland (Heym, et al., 1995), hasn't been so well studied, though all such tissues are known to have nerves. In animals such as salamanders, nerves are known to be involved in the regeneration of lost parts. Nerves are intrinsic parts of cancers, too.

About 50 years ago, a study of the production of blisters produced by hypnotic suggestion found that the blister fluid contained ATP, which had been released by sensory nerves, at the spot that had been touched by what the subject believed was a lighted cigarette. ATP also appears in the fluid of a blister caused by heat, but this example showed how important the sensory nerves are, for things beyond sending messages to the brain. Both ATP, and one of its breakdown products, adenosine, activate some enzymes involved in inflammation. ATP activates the MMP proteinase enzyme that dissolves extracellular matrix, which is a basic step in tissue remodeling, and it also activates a phospholipase which releases arachidonic acid, and the cyclooxygenase enzyme, COX-2, which converts arachidonic acid to prostaglandins.

Besides activating the enzymes to break down the extracellar structure, ATP stimulates cell division and angiogenesis, all of which are normal parts of tissue maintenance. In the bladder, stretching causes the epithelial cells to release ATP, which stimulates sensory nerves; in this situation, the epithelial cells are acting as sense organs, and the ATP acts as a neurotransmitter. It has a similar effect in the breast, in relation to milk ejection (Bowler, et al., 2001). In other tissues, such as bone, mechanical forces also release extracellular ATP, and in this situation it seems to be an important anabolic stimulus to bone growth and repair (Furuya, et al., 2004).

ATP is increasingly recognized (Burnstock, 2007) as a basic neurotransmitter or cotransmitter, but it is something more important and basic than that: it's a constant signal of any cell's presence to neighboring cells. If the concentration of ATP varies too much, it indicates that something is wrong. If a cell is injured or fails to produce enough energy, it leaks ATP. During oxygen deficiency, the leaking ATP causes vasodilation, increasing circulation, and in the respiratory center, it stimulates breathing (Buttigieg and Nurse, 2004; Conde, et al., 2012).

In the prenatal environment, lacking polyunsaturated fatty acids from the environment, ATP is involved in the orderly development of the organism, adjusting rates of growth in a coordinated way. This system, that can be seen in embryology and the early stages of gestation, has all the properties of a self-regulating control system, with a built-in intention to develop in a certain direction. The intention that Mechnikov saw in the phagocyte, is in the whole organism. Cells that will later be thought of as part of "the immune system" are present at the very early stages of embryonic development, participating in its coming into existence. There is no genetic "blueprint" that is being read out for either the organism as a whole or for an immune system that has evolved to deal with infectious challenges. The system creates and discovers its potential, in a unique way, responding to what its environment provides it.

Not long ago, following the cult of the "Weismann barrier," it was believed that oocytes were "read out" at an early stage of development, from a genetic blueprint that would never be accessible again. That doctrine lasted for 100 years, until someone tested it (Johnson, et al., 2004, 2005; Bukovsky, et al., 2005; White, et al., 2012). As they showed, the embryo and the adult are intentional unities, able to improvise in surprising ways, but genetics and immunology have created fragmentary, mechanistic descriptions of them.

During development, the coordinated growth and functioning of the system is affected by the chemicals in the environment that the organism encounters. The prostaglandins reflect a particular ecosystem in which plants produce certain unsaturated fatty acids, but biomedical ideologues have idealized them, following the doctrine that this is the environment that we evolved to live in. This is very much like the nutrition professor at Oregon State University who taught students that white bread should be included in the diet because God gave it to us.

Lacking PUFA and prostaglandins, extracellular ATP would activate constructive pathways, tending to create a new equilibrium, without producing all of the harmful effects of the prostaglandins. As unstable polyunsaturated fats accumulate in the tissues with aging, they increasingly promote vicious circles of stress (some of those were described in Fats, Functions & Malfunctions).

Recognizing a mismatch between the organism's potentials and the present environment, and suggesting ways to improve the environment, isn't anything new, and a limited form of it has been institutionalized in various offices of occupational health and safety, traffic safety, and pollution control, but it conflicts with the other well-institutionalized attitude, that people must be changed to conform to the situation as it is. Eugenics, sterilization, vaccination, health education, and publicity campaigns explaining why cancer, heart disease, and obesity are caused by choices the individual makes, are well financed and supported by large organizations.

The idea of autoimmunity epitomizes this general situation, in which reductionist theories are invoked to explain why a person is causing his own sickness. If antibodies evolved to attack microbes, then the immune system has become defective when it produces antibodies against its own tissue. But if the system of wandering cells, complement, antibodies, etc., has to do with development and maintenance of the organism, the presence of antibodies and other "immune" factors would be expected whenever a tissue is damaged.

Simply twisting a piece of cartilage has been shown to make it antigenic, and many other things causing sterile inflammation cause antibodies to appear. Strokes or other brain injuries cause antibodies to be produced. The presence of auto-antibodies has been found to facilitate the recovery from an aseptic inflammatory condition of the brain, accelerating healing and re-vascularization (Hofstetter, et al., 2003). Intravenous immunoglobulin has a long history of use to reduce inflammation (Nimmerjahn and Ravetch, 2008), and it has been tested as a treatment for heart failure, producing anti-inflammatory effects (Aukrust, et al., 2006).

Components of the complement system and C-reactive protein, which are increased by tissue injury, are involved in the anti-inflammatory clearance of dying cells (Gershov, et al., 2001).

The presence of the "essential fatty acids" is an important factor in the allergenicity of transplanted tissues (Schreiner, et al., 1988), which might be expected, from the role of the prostaglandins in creating inflammation whenever a tissue is stressed.

Many types of evidence indicate that environmental PUFA and prostaglandins produced from the "essential" fatty acids are required for inflammation to progress to degeneration. The n-9 polyunsaturated fatty acids (the kind that we can make from saturated fat or sugar) seem to be positively protective against inflammation. For example, rats fed a diet with 2% hydrogenated coconut oil for two weeks had lower levels of IL-6 and C-reactive protein than when a small amount of arachidonic acid and docosahexaenoic acid (DHA) were added. Mead acid (20:3n9) was lower in the group with the PUFA supplement,

and the inflammatory reaction to endotoxin was greater in the supplemented group (Ling, et al., 2012).

Many of the things that can be achieved by vaccination and treatment with safe anti-inflammatories such as aspirin could be done better by long-term changes of diet, and by taking into account the interactions of the hormones, especially progesterone, estrogen, and thyroid, with nutrients and stressors. But much more than that is needed: The nature of the relationships between environmental factors and the body's reactions has to be clarified, so that the processes of healing and regeneration can more closely resemble the prenatal condition, possibly even continuing in adulthood the "pedomorphic" process, realizing human potentials that haven't previously been seen.

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Ray Peat's Newsletter

"... a meaningful model of Life has to exclude Randomness." G. Zajicek

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When energy fails: Edema, hypertension, heart failure sarcopenia, cramps, etc.

More than 100 years ago the idea of a morphogenetic field was proposed by A.G. Gurwitsch, as a way to explain the orderly movements of cells in embryos and growing tissues, and to understand the principles that cause cells to change appropriately when their location in the organism changes. For 30 years, the concept guided research in embryology, but also led to important discoveries in the biology of cancer, aging, wound repair, and other important areas. But by the late 1940s, a more abstract approach to biology, based on the gene doctrine of Mendel and Weismann, took charge of academic and governmental biological research. This ideology at first said that organisms are determined by unchanging units of inheritance, "genes," and later when genes were found to be susceptible to mutation, the changes were said to be always random. The Central Dogma of the ideology was that any meaningful, adaptive changes that occur in an organism can't influence the genes. For many years, adaptive changes were said to be nothing but changes in the size or function of existing cells, because the cells of the major organs of the body were supposed to be created before birth, or in infancy.

Besides the purely ideological commitment to the theory of genes, there were other influences that contributed to the culture of Molecular Biology. People learned histology from slides or pictures made by killing, hardening, dehydrating, and slicing parts of organisms. Biochemists studied the chemistry of life mainly by grinding cells or tissues, and extracting water soluble materials to study the actions of enzymes on various materials. These unrealistic artifacts filled the textbooks and the minds of generations of biologists and physicians. The culture of molecular biology used these artifacts to create theories of embryology and physiology, and holistic ideas such as the developmental field were disregarded.

The mental image of a living organism that has been created by that culture is simply wrong. The concept of a developmental field is essential for understanding embryology, because things that exist on a scale bigger than molecules and cells govern the functions of the molecules and cells, and the principles of embryology don't arbitrarily stop operating at birth, but can be seen to continue operating during maturity and aging. The interactions of cells with their environment are different at different stages of life, but there are commonalities that are extremely important.

The processes that govern the pregnant woman's blood circulation, in sustaining the development of a fetus, are very similar to the processes that govern anyone's blood circulation, providing for the maintenance and renewal of all the body's organs. The common problems of pregnancy involving the circulatory system can provide insights into the problems of the various organs that have been the focus of the medical specialties, and into some basic medical issues, including aging, obesity, and inflammation.

The development of a fertilized egg into an embryo consumes energy at a very high rate, and the way the embryo develops depends on a continuously adequate supply of oxygen and sugar, and other nutrients. The intense flow of energy through each stage of a developing structure shapes the following stage. The necessary energy and materials are provided abundantly by the mother's blood. When the development has advanced far enough to make life possible outside the uterus, energy will be used more slowly, for growth, maintenance, and renewal of tissues.

Failure to renew cells and tissues leads to the loss of function and substance. Bones and muscles get weaker and smaller with aging. Diminished bone substance, osteopenia, is paralleled, at roughly the same rate, by the progressive loss of muscle mass, sarcopenia (or myopenia). The structure of aging tissue changes, with collagen tending to fill the spaces left by the disappearing cells. It's also common for fat cells to increase, as muscle cells disappear.

When conditions are ideal, as during healthy development in the uterus, tissue damage is corrected by the multiplication of cells to replace any that were lost. But when conditions are less perfect, injuries are imperfectly repaired, usually with highly collagenous scar tissue bridging the area that was destroyed. During this imperfect repair, there is inflammation, which apparently exists to the extent that the substances needed for regeneration are lacking. For example, when oxygen is lacking, lactic acid is likely to be produced, along with increases of pro-inflammatory regulators such as histamine and serotonin, leading to the loss of many important proteins and functions, and the over-production of collagen instead.

Since cellular renewal of tissues, in a healthy individual, is a constant process, we can think of the metabolic rate of a healthy adult as just what is needed to sustain this constant, limited sort of regeneration, but not quite intense enough to produce scarless healing of a wound (without special intervention).

If something reduces the systemic ability to produce energy, there will be a gap between the available energy and the energy needed for the constant turnover of cells in each tissue and organ, and a generalized inflammation will develop. The replacement of cells will be slowed, and the organism will mobilize the processes used for producing scar tissue, producing an excess of collagen, filling the spaces left by the lost cells.

We are susceptible to many things that interfere with energy production—the substitution of iron for copper in the respiratory enzyme, the absorption of endotoxin, the accumulation of PUFA, a deficiency of thyroid hormone, the formation of increased amounts of nitric oxide, serotonin, and histamine, etc. Different environments will condition the way the defensive mechanisms of inflammation are produced.

Toxemia of pregnancy, or preeclampsia, is a state of generalized inflammation, and some of the causes and remedies are known. Despite the predominance of crazy genetic theories of preeclampsia in 20th century medical literature, there was clear evidence (reviewed by Tom Brewer, Douglas Shanklin, and Jay Hodin) that it was caused by malnutrition, and that it could be cured by adequate protein, salt, and calcium.

The old medical practice of restricting salt intake during pregnancy was an important factor in causing it, so it's interesting to look at the effects of salt restriction as a treatment for hypertension.

The pregnant woman's blood volume expands, to permit the supply of energy to match the needs of the embryo. If the blood volume doesn't increase, or if it decreases, as in pregnancy toxemia, her blood pressure will increase. Typically, the decrease of blood volume is accompanied by an increase in the extracellular fluid, edema, resulting from leakage of fluid through the walls of the capillaries, and albumin appears in the urine as it leaks through the capillaries in the kidneys. The amount of blood pumped by the heart, however, is increased in toxemia (Hamilton, 1952), showing that the increased blood pressure is at least partially compensating for the smaller volume of blood.

A similar situation, reduced blood volume and edema, can be seen (Tarazi, 1976) in "essential hypertension," the "unexplained" high blood pressure that occurs more often with increasing age and obesity. At the beginning of "essential hypertension," the amount of blood pumped is usually greater than normal.

In both situations, preeclampsia and essential hypertension, there is an increased amount of aldosterone, an adrenal steroid which allows the kidneys to retain sodium, and to lose potassium and ammonium instead. A restriction of salt in the diet causes more aldosterone to be produced, and increased salt in the diet causes aldosterone to decrease. One effect of aldosterone is to increase the production of a substance called vascular

endothelial growth factor, VEGF, or vascular permeability factor, which causes capillaries to become leaky, and causes new blood vessels to grow.

While increased salt in the diet tends to lower both aldosterone and VEGF, reducing the leakiness of blood vessels, sodium also has a direct effect that tends to prevent the leakage of water and albumin out of the blood vessels, helping to maintain the blood volume which is needed to perfuse the kidneys, preventing them from producing signals to increase blood pressure and aldosterone. There is a large amount of albumin in the blood serum, and sodium ions associate with the negative electrical charges on the albumin molecule. This association causes the complex of albumin and sodium to attract a large amount of water, that is to exert osmotic or oncotic pressure. This oncotic pressure causes any excess extracellular water to be attracted into the blood vessels, preventing edema while maintaining the blood volume. When there is too little sodium, the albumin molecule itself easily leaves the blood stream along with the water.

Instead of considering the significance of sodium's effects on albumin, aldosterone, and VEGF, textbooks have often talked about the factors that "pump" sodium, and factors that specifically regulate the movement of water. Experiments in which an excess of aldosterone is combined with a high salt intake produce increased blood pressure, and--by invoking various genes--salt is said to cause hypertension in certain people. This reasoning is hardly different from the reasoning of the drug companies in the 1950s who said that since women with toxemia have hypertension and edema, they should be treated with a diuretic and a low salt diet, to eliminate water and to reduce blood pressure.

The physiological loss of sodium occurs when energy metabolism fails, as in diabetes, hypothyroidism, hyperestrogenism, and starvation. What these conditions have in common is an increased level of free fatty acids in the blood. Increased free fatty acids impair the use of glucose. The consumption of carbohydrate, like an increase of thyroid hormone, insulin, or progesterone, increases the retention of sodium; fructose is the most effective carbohydrate (Rebello, et al., 1983).

The loss of sodium is often accompanied by the retention of water, reducing the osmotic pressure of the body fluids. The leakiness of blood vessels allows the extracellular fluid volume to increase, as understood in the standard definition of edema. However, when this fluid is hypo-osmotic, it will enter cells, causing them to swell. Cell swelling excites cells (Ayus, et al., 2008; Baxter, et al., 1991), and can kill them if they are unable to produce enough energy to restore their original volume, by measures including the excretion of amino acids and potassium. Both low sodium (hyponatremia) and low osmotic pressure stimulate the adrenergic nervous system.

The increase of adrenalin, caused by a deficiency of sodium, is one of the factors that can increase blood pressure; if the tissues's glycogen stores are depleted, the adrenalin will mobilize free fatty acids from the tissues, which tends to inhibit energy production from glucose, and to increase leakiness. After I had read Tom Brewer's work on preventing or curing preeclampsia with added salt, I realized that the premenstrual syndrome involved some of the features of preeclampsia (edema, insomnia, cramps, hypertension, salt craving), so I suggested to a friend that she might try salting her food to taste, instead of trying to restrict salt to "prevent edema." She immediately noticed that it prevented her monthly edema problem. For several years, all the women who tried it had similarly good results, and often mentioned that their sleep improved. I mentioned this to several people with sleep problems, and regardless of age, their sleep improved when they ate as much salt as they wanted. Around that time, several studies had shown that salt restriction increases adrenalin, and one study showed that most old people on a low sodium diet suffered from insomnia, and had unusually high adrenalin. When they ate a normal amount of salt, their adrenalin was normalized, and they slept better.

It's very common for physicians who are aware of progesterone's "anti-aldosterone" activity to think that both estrogen and progesterone are responsible for the increased risk of sodium loss in women, especially during pregnancy, but Hans

Selye demonstrated that progesterone will normalize sodium retention even when there is no aldosterone at all, following removal of the adrenal glands. It is estrogen which is responsible for the dangerous loss of sodium.

The ratio of estrogen to progesterone—regardless of age or gender—is an important factor in regulating minerals and water, cell energy metabolism, and blood pressure. The ratios of many other regulatory substances (including serotonin/dopamine, glucagon/insulin, and aldosterone/cortisol+progesterone) vary according to the quality of the individual's level of adaptation to the environment. Improving the environment can shift the ratio in the direction of restoration, rather than mere survival.

Gershom Zajicek and his colleagues have demonstrated an organized renewal of tissues, in which new cells are born with the division of stem cells, and "stream" away from their origin as they mature, and finally are shed or dissolved. A few studies have demonstrated a similar kind of migration of new cells in the brain (Eriksson, et al., 1998; Gould, et al., 1999), a process which differs by the absence of systematic dissolution of mature brain cells. While Zajicek has demonstrated the conversion of one kind of cell, such as a pancreatic ductal epithelial or acinar cell into insulin-secreting beta cells, other researchers have shown that after injury to the pancreas beta cells can be formed from glucagon-secreting alpha cells, as well as from other beta cells.

Stress, increasing the need for energy, increases the formation of cortisol and free fatty acids when glucose isn't available, and those—while they provide alternative sources of energy—interfere with the ability to produce energy from glucose. Free fatty acids and cortisol can cause the insulin-secreting beta cells to die. Glucose, and insulin which allows glucose to be used for energy production, while it lowers the formation of free fatty acids, promote the regeneration of the beta-cells. Although several research groups have demonstrated the important role of glucose in regeneration of the pancreas, and many other groups have demonstrated the destructive effect of free fatty acids on the beta cells, the mainstream medical culture still claims that "sugar causes diabetes."

In the adrenal glands, renewing cells stream from the capsule on the surface of the gland toward the center of the gland. The first cells to be produced in a regenerating gland are those that produce aldosterone, the next in the stream are the cortisol producing cells, and the last to be formed are the cells that produce the sex hormones, the androgens including DHEA, and progesterone. In aging, after the age of thirty, the renewal slows, but the dissolution of the sex hormone zone continues, so the proportion shifts, increasing the ratio of the aldosterone and cortisol producing cells to the layer that produces the protective androgens and progesterone (Parker, et al., 1997).

Even before aldosterone was identified, progesterone's role in regulating the salts, water, and energy metabolism was known, and after the functions of aldosterone were identified, progesterone was found to protect against its harmful effects, as it protects against an excess of cortisol, estrogen, or the androgens. New anti-aldosterone drugs are available that are effective for treating hypertension and heart failure, and their similarity to progesterone is recognized.

While stress typically causes the adrenal glands to produce cortisol, extreme stress, as described by Hans Selye, damages the adrenal cortex, and can cause the cells to die, leading to the death of the animal. There is evidence that it is the breakdown of unsaturated fatty acids that causes damage to the adrenal cortex in extreme stress. Although many factors influence the production of the adrenal steroids, arachidonic acid, even without being converted to prostaglandins, is an important activator of aldosterone synthesis. Adrenalin, produced in response to a lack of glucose, liberates free fatty acids from the tissues, so when the tissues contain large amounts of the polyunsaturated fatty acids, the production of aldosterone will be greater than it would be otherwise.

The continuing accumulation of polyunsaturated fats in the tissues is undoubtedly important in the changing relationship between the pancreas and the adrenal glands in aging. Aspirin, which is antilipolytic, decreasing the release of free fatty

acids, as well as inhibiting their conversion to prostaglandins, lowers the production of stress-induced aldosterone, and helps to lower blood pressure, if it's taken in the evening, to prevent the increase of free fatty acids during the night. Aspirin increases insulin sensitivity. A low salt diet increases the free fatty acids, leading to insulin resistance, and contributing to atherosclerosis (Prada, et al., 2000; Mrnka, et al., 2000; Catanozi, et al., 2003; Garg, et al., 2011).

The same factors that support or interfere with cellular renewal in the pancreas and adrenal glands have similar effects in the bones, skin, skeletal and heart muscle, nervous system, liver, and other organs. In every case, the local circulation of blood is influenced by both local and systemic factors. The loss of control over the water in the body is the result of energy failure, and hypertension is one of the adaptations that helps to preserve or restore energy production.

Lowering inflammation and the associated excess of free fatty acids in the blood, and improving the ability to oxidize glucose, will lower blood pressure while improving tissue renewal, but lowering blood pressure without improving energy production and use will create new problems or intensify existing problems. After 40 years the medical profession quietly retreated from their catastrophic approach to pregnancy toxemia, but in the more general problem of essential hypertension, the mistaken ideology is being preserved, even as less harmful treatments are introduced. That ideology prevents a comprehensive and rational approach to the problems of stress and aging.

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Contents:

Steroids
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Steroids

By Raymond Peat, Ph.D.

This type of molecule might be the most common carbon compound in the universe. It is made by single celled organisms, by plants, and by animals, and has many kinds of function. The steroid hormones are involved in all aspects of animal physiology, and overlap with control functions of the nervous system, peptide hormones, metabolites, prostaglandins, cyclic nucleotides, etc. Sometimes people speak of "steroids" when they mean glucocorticoids such as cortisol or a synthetic like dexamethasone, or, among athletes, when they mean anabolic steroids or synthetic androgens; and so it is common to associate "steroids" with harmful side effects. All foods contain steroids and sterols (a major type, containing an alcohol group and a side-chain) some of which are beneficial and some of which are toxic or allergenic.

In animals, cholesterol is the basic sterol molecule, which is massively converted into other substances, including the steroid hormones. Thyroid hormone and vitamin A are required for this conversion. The first step occurs in the energy-producing mitochondrion, where cholesterol loses its side-chain and is slightly oxidized, producing pregnenolone. Being less fat soluble than cholesterol, pregnenolone leaves the mitochondrion, so it can't inhibit its own synthesis. Rather, it seems to stimulate its own synthesis, though this isn't as clearly established as in the case of progesterone.

Depending on the tissue, pregnenolone will be converted by enzymes in the cytoplasm into either progesterone or DHEA (Also called DHA, dehydroepiandrosterone). The fact that progesterone (and probably pregnenolone) stimulates its own synthesis means that taking it does not suppress the body's ability to synthesize it, as happens with cortisol. Sometimes, one dose or a few doses can restore the body's ability to produce enough of its own.

Progesterone also allows the thyroid gland to secrete its hormones, especially when the thyroid function has been inhibited by estrogen. Since the thyroid hormone is needed to produce progesterone, a supplement of either tends to normalize both thyroid and progesterone production.

Progesterone and DHEA are the precursors for the other more specialized steroid hormones, including cortisol, aldosterone (sodium-retaining hormone), estrogen, and testosterone. The formation of these other hormones is tightly regulated, so that taking the precursor will correct a deficiency of a specialized hormone, but will not create an excess. At least in the case of progesterone, an excess tends to balance or neutralize an excess of the specialized hormone, so it has been described as having anti-androgenic, anti-estrogen, ant-aldosterone, and anti-cortisol functions.

Many steroids have a protective ("catatoxic") action against a wide variety of poisons. Some of the quick effects (e.g., within 10 minutes) of progesterone and pregnenolone probably represent a catatoxic action, as well as a neutralizing or balancing of excessive estrogen or cortisol. Improved metabolic efficiency, sparing oxygen and glucose, will have a quick effect in reducing edema.

> **"All foods contain steroids and sterols... some of which are beneficial and some of which are toxic..."**

During pregnancy, very large amounts of progesterone are made. It protects and stabilizes practically all functions of both the mother and the fetus. Progesterone, glucose and the thyroid hormones powerfully influence the brain development and intelligence of the baby, probably by influencing both the number and the size of brain cells, and the quality of their functioning.

Part of progesterone's protective effect is a result of its quieting effect on cells. For example, it tends to prevent seizure activity in brain cells. During childbirth, its normal function is to act as an anesthetic. When the level of estrogen is too high, progesterone can't achieve this effect. In a non-pregnant person, it is important to determine the minimum effective dose by taking only a few drops at a

time, and repeating this small dose about every 20 minutes until symptoms have been controlled. Otherwise, serious "drunkenness" can be produced, with loss of coordination, and even unconsciousness.

The only solvent for progesterone which isn't toxic and which will dissolve an effective quantity, is vitamin E. In this form, it can be absorbed through the skin or other membranes, or can be taken orally. Taken orally, it is absorbed as chylomicrons, going into the general circulation (as vitamin E does), instead of to the liver where it would be prepared for excretion. In this form, therefore, it is fully and quickly available to all tissues. It is approximately 20 times more powerful in its action than other preparations, so it is important to use it in physiological quantities, rather than in the huge doses commonly given rectally or by injection. Ten or 20 mg. is often an effective dose, though people with low thyroid or high estrogen sometimes use 50 to 100 mg. per day. In the customary 10% solution, one drop contains about 3 mg. progesterone, and 1 ml. (1/4 tsp.) contains 100 mg. The first dose should never be more than 15 mg. (An ounce of 10% progesterone in vitamin E is $15; a dozen one-ounce bottles is $144.)

Pregnenolone, taken orally, does nothing noticeable to a healthy animal or person, but if the stress-related hormones are elevated, they return to normal when pregnenolone is taken. The brain contains much more pregnenolone, DHEA, and progesterone than do other organs or the blood, and these levels decrease progressively with age. Older people are more likely to feel an effect from pregnenolone, than are young people. (A ten gram bottle of pregnenolone is $20; 1/4 kg. is $250. A tenth of a gram is a reasonable first dose, though some people seem to need as much as 1 gram per day.)

Thyroid

By Raymond Peat, Ph.D.

Measuring the amount of thyroid in the blood isn't a good way to evaluate adequacy of thyroid function, since the response of tissues to the hormone can be suppressed (for example, by unsaturated fats).

In the 1930's accurate diagnosis was made by evaluating a variety of indications, including basal oxygen consumption, serum cholesterol level, pulse rate, temperature, carotenemia, bowel function, and quality of hair and skin. A good estimate can be made using only the temperature and pulse rate.

Oral or armpit temperature, in the morning before getting out of bed, should be around 98° F, and it should rise to 98.6° by mid-morning. This is not valid of you sleep under an electric blanket, or if the weather is hot and humid. A person who is hypothyroid produces heat at a low rate, but doesn't lose it at the normal rate, since there is less sweating, and the skin is relatively cool. Many hypothyroid people compensate with high adrenalin production (sometimes 40 times higher than normal), and this tends to keep the skin cool, especially on the hands, feet, and nose. The high adrenalin is the consequence of low blood glucose, so a feeding of carbohydrate, such as a glass of orange juice, will sometimes lower the pulse rate momentarily. Healthy populations have an average resting pulse rate of about 85 per minute. Especially in hot weather it is useful to consider both temperature and pulse rate.

The Achilles tendon reflex is another quick way to estimate thyroid function. This reflex is used because of the insignificant weight of the toes in relation to contraction of the gastrocnemius muscle. The T (repolarization) wave on the electrocardiogram is a similar indicator of the rate of energy production. Thumping the Achilles tendon causes the muscle to contract (unless it is already in a semi-contracted state, which isn't uncommon). The contraction consumes energy, and the muscle can't relax until enough energy has been produced to restore the threshold and the readiness for a new contraction.

"Healthy populations have an average pulse rate of about 85 per minute."

If energy production is efficient, relaxation is faster than the passive return motion of the foot, so the foot swings freely back to its original position, and over shoots slightly, causing a slight swinging action. In hypothyroidism, the foot returns as if controlled by a pneumatic door-closer, and settles slowly and precisely into its relaxed position, sometimes with a hesitating, intermittent motion. This slow replenishment of energy, and slow relaxation, can cause muscles to cramp easily. The aching leg muscles of children at the end of an active day are often a sign of hypothyroidism, and sometimes the gastrocnemius muscle becomes very swollen and hypertrophied in hypothyroid children. The same process, of slow energy regeneration, can cause rhythm disturbance in the heart, and often causes insomnia and restless sleep.

The thyroid gland secretes about 3 parts of thyroxin to one part of triiodothyronine, and this allows the liver to regulate thyroid function, by converting more of the T4 to the active T3 when there is an abundance of energy. Glucose is essential for the conversion, so during fasting there is a sharp decrease in metabolic rate, and in experiments, 200 or 300 calories of carbohydrates can be added to the diet without causing fat storage.

When the liver is the main cause of hypothyroidism, your temperature (and especially the temperature of your nose, hands and feet) will fall when you are hungry, and will rise when you eat carbohydrates. If a hypothyroid person has a very slow pulse, and feels lethargic, it seems that there is little adrenalin; in this case, a feeding of carbohydrate is likely to increase both the pulse rate and the temperature, as the liver is permitted to form the active T3 hormone.

Women often have above-average thyroxin, with symptoms of hypothyroidism. This is apparently because it isn't being converted to the active form (T3). Before using a Cytomel (T3) supplement, it might be possible to solve the problem with diet alone. A piece of fruit or a glass of juice or milk between meals, and adequate animal protein (or potato protein) in the diet is sometimes enough to allow the liver to produce the hormone. If Cytomel is used, it is efficient to approximate the physiological rate of T3 formation, by nibbling one (10 or 25 mcg.) tablet during the day. When a large amount is taken at one time, the liver is likely to convert much of it to the inactive reverse-T3 form, in a normal defensive response.

Women normally have less active livers than men do. Estrogen can have a directly toxic effect on the liver, but the normal reason for the difference is probably that temperature and thyroid function strongly influence the liver, and are generally lower in women than in men. Estrogen inhibits the secretion of hormone by the thyroid gland itself, probably by inhibiting the proteolytic enzyme which dissolves the colloid. Progesterone has the opposite effect, promoting the release of the hormones from the gland. At puberty, in pregnancy, and at menopause, the thyroid gland often enlarges, probably as a result of estrogen dominance.

Thyroid function stimulates the liver to inactivate estrogen for secretion, so estrogen dominance can create a vicious circle, in which excess estrogen (or deficient progesterone) blocks thyroid secretion, causing the liver to allow estrogen to accumulate to even higher levels. Progesterone (even one dose, in some causes) can break the cycle. However, if the gland is very big, the person can experience a few months of hyperthyroidism, as the gland returns to normal. It is better to allow the enlarged gland to shrink more slowly by using a thyroid supplement. If an enlarged gland does begin to secrete too much thyroid hormone, it can be controlled with tablets of propylthiouracil, or even with raw cabbage or cabbage juice, and cysteine-rich meats, including liver.

Besides fasting, or chronic protein deficiency, the common causes of hypothyroidism are excessive stress or "aerobic" (i.e., anaerobic) exercise, and diets containing beans, lentils, nuts, unsaturated fats (including carotene), and undercooked broccoli, cauliflower, cabbage, or mustard greens. Many health conscious people become hypothyroid with a synergistic program of undercooked vegetables, legumes instead of animal proteins, oils instead of butter, carotene instead of vitamin A, and breathless exercise instead of a stimulating life.

3 : 1

T4 : T3

Si hypo à cause de foie = Temp° ↓ quand tu as faim (nez, main, pied) et ↑ si tu manges

Si hyp à faible FC et se sent léthargique ca veut dire pas assez d'adrénaline. Si prend carbs ca ↑ Temp et FC. Car le foie recommence à faire du T3

Du lait entre les repas, protéine de patate, va stimuler le foie à produire T3

Thyroi stimule le foie à à innactiver lestro pour l'élimination sauf que lestro inhibe la thyroi qui elle est necessaire pour stimuler le foie.

propylthiouracil ou chou cru jus de chou + cystéine + du foie inhibe thyroïde

of oestroprogestins due to their effects on metabolic parameters. As shown by prescription for contraceptive use, **replacement therapy with oral synthetic oestrogens induces a diabetogenic tendency as well as hypertensive, dyslipidaemic and thrombogenic risks,** especially when associated with progestins issued from nortestosterone. Reducing the oestrogen doses, using equine sulfoconjugates and selecting non-androgenic progestins has already minimized these deleterious effects. The present availability of oral or percutaneous natural 17 beta oestradiol and of norpregnanes calls for reconsideration of the glucidic risk due to oestroprogestin prescription. A few studies have already shown that in fact they can improve glucose tolerance. The recommended substitution of menopause to prevent atherosclerosis must lead to a better characterization of its glycaemic and insulinaemic effects.

"Effects of oral contraceptives on carbohydrate and lipid metabolisms in a healthy population: the Telecom study," Simon D; Senan C; Garnier P; Saint-Paul M; Garat E; Thibult N; Papoz L, Am J Obstet Gynecol, 1990 Jul, 163:1 Pt 2, 382-7. "In a cross-sectional study that aimed to identify risk factors for diabetes, 1290 consecutive, healthy, nonpregnant women of child-bearing age were examined in a center for preventive medicine. An in-depth interview about menses, use of oral contraceptives, and menopause was performed. Plasma glucose at fasting and 2 hours after a 75 gm glucose load, glycated hemoglobin A1c, fasting plasma insulin, total plasma cholesterol, and triglycerides were measured. Compared with nonusers taking no progestogens, oral contraceptive users (n = 431; 33.4%) were younger (p less than 0.001) and leaner (p less than 0.001). After adjustment for age and body mass index, oral contraceptive users had higher 2-hour plasma glucose (p less than 0.001), higher fasting plasma insulin (p less than 0.01), and higher triglycerides levels (p less than 0.01). Fasting plasma glucose, glycated hemoglobin A1c, and total cholesterol did not significantly differ between the two groups. In relation to dosage and types of steroid components, few differences have been found between high-dose and low-dose oral contraceptives or according to the estrogen-progestogen balance of the preparations. Use of oral contraceptives **appears to induce an increase of insulin-resistance markers, which have recently been cited as risk factors for ischemic vascular diseases.** These markers should be carefully monitored in oral contraceptive users.

"Effect of estrogen on hyperprolactinemia-induced glucose intolerance in SHN mice," Matsuda M; Mori T, *Proc Soc Exp Biol Med,* 1996 Jul, 212:3, 243-7. "The effects of prolactin (PRL) on circulating levels of glucose and insulin, and of estradiol on hyperprolactinemia-indu ced glucose intolerance of tissues were studied in pituitary-grafted SHN mice (PG mice) and sham-operated controls. Pituitary grafting (PG) decreased blood glucose levels in male mice at 1 and 3 months after the operation but did not alter those in females. PG had little effect on serum insulin levels in males, but increased those in females. In female mice at 2 months after PG, blood glucose levels were significantly higher at 1, 2, and 4 hr after glucose load when compared with those in controls. In contrast, there was no significant difference in blood glucose levels after glucose load between male PG and control mice. The rate at which blood glucose levels decreased was slower in female PG mice than in controls during the 30 min after insulin injection, whereas there was no difference in the rate after insulin injection between male PG and control mice. In ovariectomized (Ovx) mice, no significant difference was found in the blood glucose levels after a glucose load between PG and control groups at 2 months after PG. In Ovx mice treated daily with estrogen, however, a PG-dependent high level of blood glucose was observed after glucose load. These results **suggest that hyperprolactinemia decreases glucose tolerance via an increase in insulin resistance in female SHN mice and that estrogen is essential to the expression of the PRL effect."**

NOTICE THE PROPAGANDISTIC USE OF SAFFLOWER OIL AS THE CONTROL DIET: "Dietary fish oil delays puberty in female rats," Zhang Z; Benson B; Logan JL, *Biol Reprod,* 1992 Dec, 47:6, 998-1003. "Marine oils contain eicosapentaenoic acid, a fatty acid that competes for cyclooxygenase and reduces the synthesis of dienoic prostanoids including prostaglandin E2 (PGE2). Since PGE2 plays an important role in the estrogen-stimulated release of hypothalamic GnRH on proestrus, it was postulated that a diet containing fish oil would delay first ovulation through inhibitory effects on GnRH release. Thirty, 22-day-old female Sprague-Dawley rats were fed a diet containing fish oil ad libitum. **Controls were pair-fed an identical diet with the substitution of safflower oil as the dietary fat.** All rats were killed on the morning of first metestrus after vaginal opening and the display of an estrous smear(s). Fish oil feeding did not affect growth as indicated by the lack of an observed effect on body weights or femur lengths. On the other hand, pituitary, ovarian, and uterine weights were significantly lower in the rats fed fish oil ($p < 0.001$). The age at first estrus of the rats fed fish oil was significantly increased compared with the controls (42.9 +/- 1.0 vs. 36.1 +/- 0.3 days; $p < 0.001$), whereas the number of rats with corpora lutea (CL), as well as the number of CL per ovary (2.3 +/- 0.4 vs 4.8 +/- 0.6 for controls; $p < 0.001$) was significantly reduced by fish oil feeding. GnRH concentration in the preoptic area/hypothalamus was significantly increased in the fish oil-fed rats (21.4 +/- 4.0 pg/mg vs. 7.6 +/- 2.2 pg/mg for controls; $p < 0.01$); radioimmunoassable hypothalamic PGE2 was concomitantly reduced ...."

"Effects of androgens on haemostasis," Winkler UH, Maturitas, 1996 Jul, 24:3, 147-55. **"Androgen deficiency is associated with an increased incidence of cardiovascular disease. There is evidence that thromboembolic disease as well as myocardial infarction in hypogonadic males are mediated by low baseline fibrinolytic activity.**

Hypogonadism in males is associated with an enhancement of fibrinolytic inhibition via increased synthesis of the plasminogen activator inhibitor PAI 1."

"Progesterone production from granulosa cells of individual human follicles derived from diabetic and nondiabetic subjects," Diamond MP; Lavy G; Polan ML, *Int J Fertil,* 1989 May-Jun, 34:3, 204-8. "Insulin and insulin-like growth factors have been implicated in the stimulation of ovarian steroidogenesis. To assess the effect of diabetes mellitus on this process, a comparison was made of progesterone production by cultured granulosa cells (50,000 cells/well) from 11 **individual follicles of nondiabetic and 6 individual follicles of diabetic women.** Diabetic metabolic control was fair [HbA1C 6.8, 8.7 (nl 5.0-7.5)]. Cells were collected by laparoscopic follicular aspiration after ovulation induction and isolated by Percoll gradient centrifugation. Progesterone production was measured after culture with hCG (10 IU/mL) or insulin (100 microU/mL). In both nondiabetic and diabetic groups on day 4, hCG significantly stimulated progesterone production (1,686 +/- 1,268 ng/mL to 4,123 +/- 2,825 ng/mL and 1,059 +/- 249 ng/mL to 1,506 +/- 245 ng/mL, respectively). **In nondiabetic follicles, insulin also stimulated progesterone production on days 4 (2366 +/- 1032 ng/mL to 3699 +/- 1582 ng/mL; P less than .05) and 7 (987 +/- 475 ng/mL to 1858 +/- 929 ng/mL; P less than .05); this response was not noted in diabetic granulosa cells. We suggest that insulin-stimulated progesterone production by granulosa cells isolated in the presence of fair diabetic metabolic control is impaired."**

"Breast cancer risk in rats fed a diet high in n-6 polyunsaturated fatty acids during pregnancy," Hilakivi-Clarke L; Onojafe I; Raygada M; Cho E; Clarke R; Lippman ME, *J Natl Cancer Inst,* 1996 Dec 18, 88:24, 1821-7. **"...Since a high-fat diet may increase circulating estrogen levels** and possibly breast cancer risk, dietary factors during pregnancy could influence the risk of developing this disease." "Pregnant or virgin female Sprague-Dawley rats that had been previously treated with 10 mg 7, 12-dimethylbenz[a]anthracene (DMBA) by oral gavage when 55 days old were assigned to one of two isocaloric diets containing either 16% calories from fat (low-fat) or 43% calories from fat (high-fat) for the length of pregnancy or for the equivalent time of approximately 21 days. There were 20 pregnant and 10 nonpregnant DMBA-treated rats per group. Ten additional pregnant animals (not previously treated with DMBA) per group were used for hormone analysis. **The fat source used was corn oil, which is high in n-6 polyunsaturated fatty acids, primarily linoleic acid.** The animals were checked for tumors at least once per week by palpation. The tumor size, number, and latency to appearance after carcinogen exposure were recorded. The statistical significance of observed differences was tested by use of appropriate two-sided tests. RESULTS: Female rats on different diets had virtually identical food intakes and weight gains during pregnancy. **On gestation day 19, serum estradiol levels were approximately twofold higher in rats fed a high-fat diet than in rats fed a low-fat diet (P < .02).** The serum insulin levels and insulin/glucose ratios (an index of insulin resistance) in rats fed the high-fat diet were approximately twofold lower than in rats fed the low-fat diet, but the differences did not reach statistical significance (P < .09 and P < .09, respectively). On week 18 following DMBA administration, the number of rats developing mammary tumors was significantly higher in the group exposed to a high-fat diet (40% of animals) than in the group exposed to a low-fat diet (10% of animals) during pregnancy (P < .05). Tumor multiplicity, latency to tumor appearance, and size of tumors upon first detection were similar among the dietary groups. No intergroup differences in the mammary tumor incidence were noted in virgin animals that were exposed to the high- or low-fat diets for an equivalent period of time. CONCLUSIONS: **Our findings indicate that consumption of a diet high in fat (primarily in the form of n-6 polyunsaturated fatty acids) during pregnancy increases the risk of developing carcinogen-induced mammary tumors, possibly by increasing the pregnancy levels of circulating estrogens.** IMPLICATIONS: If further studies find that the results from animal model studies are applicable to humans, some human breast cancers may be preventable by dietary manipulations during pregnancy."

Metabolism of glomerular basement membrane in normal, hypophysectomized, and growth-hormone-treated diabetic rats," Reddi AS, *Exp Mol Pathol,* 1985 Oct, 43:2, 196-208. "The in vivo synthesis of the renal **glomerular basement membrane (GBM)** collagen was studied in **normal, hypophysectomized (hypox), diabetic, and growth-hormone (GH)-treated diabetic rats....**" "A significant decrease in both proline and hydroxyproline specific activities were observed in GBM of hypox rats at all periods of study. Administration of GH to hypox rats returned the GBM collagen synthesis to normal. Diabetic GBM had higher proline and hydroxyproline specific activities when compared to normal rats. **Treatment of diabetic rats with GH for 10 days further increased both proline and hydroxyproline specific activities when compared either to diabetic or normal rats treated with GH.** The activity of glucosyltransferase, an enzyme involved in the biosynthesis of the disaccharide unit of GBM collagen was found to be decreased in glomeruli of hypox rats. In contrast, the activity of N-acetyl-beta-glucosaminidase, a glycoprotein-degrading enzyme, was found to be significantly increased in hypox rats. GH treatment restored both enzyme activities to normal. The results of the present study show that **GBM collagen synthesis is decreased in hypox rats and increased in diabetic rats.** not only normalized GBM collagen synthesis in hypox rats but also caused significant increase in diabetic rats. This suggests that the renal GBM metabolism is influenced by GH, and this may be of particular significance in view of GH involvement in diabetic microvascular complications."

Ray Peat's Newsletter

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Progesterone, not estrogen, is the coronary protection factor of women.

In the 1940s, around the time that Hans Selye was reporting that estrogen causes shock, and that progesterone protects against many stress-related problems, the anthropologist Ashley Montague published *The Natural Superiority of Women.* Later, as I looked at the history of endocrine research, it seemed apparent that progesterone was responsible for many of the biological advantages of females, such as a longer average life-span, while testosterone was responsible for men's advantage in muscular strength.

Although evidence of estrogen's toxicity had been accumulating for decades, pharmaceutical promotion was finding hundreds of things to treat with estrogen, which they called "the female hormone." By the 1940s, it was known to produce excessive blood clotting, miscarriage, cancer, age-like changes in connective tissue, premenstrual syndrome, varicose veins, orthostatic hypotension, etc., but, as Mark Twain said, a lie can run around the world before the truth gets its boots on.

After the DES fiasco, in which "the female hormone" which had been sold to prevent miscarriages was proven to cause them, the estrogen industry decided to offer men the protection against heart attacks that women supposedly got from their estrogen. The men who received estrogen in the study had an increased incidence of heart attacks, so that campaign was postponed for about 30 years.

The Shutes used vitamin E to treat the excessive blood clotting caused by estrogen, and vitamin E was considered to be an estrogen antagonist. Estrogen affected the liver's production of clot-regulating proteins, and it also relaxed large veins, allowing blood pooling that slowed the blood sufficiently to give it time to form clots before returning to the lungs. Early in the century, unsaturated fats were found to inactivate the proteolytic enzymes that dissolve clots, and vitamin E was known, by the 1940s, to provide protection against the toxicity of the unsaturated fats. The toxic synergy of estrogen and unsaturated fats had already been recognized.

But in the 1950s, the seed oil industry, ignoring the toxic, carcinogenic effects of the unsaturated oils, began intensified promotion of their products as beneficial foods. (Decades earlier, Mark Twain had reported on the plans of the cottonseed industry to make people eat their by-product instead of butter.)

While estrogen was being offered as the hormone that protects against heart attacks, the liquid vegetable oils were being advertised as the food that would prevent heart attacks. Just a few years after the estrogen industry suffered the setbacks of the DES and heart attack publicity, the oil industry cancelled some tests of the "heart protective diet," because it was causing both more heart attacks and more cancer deaths.

Complex issues in physiology can be simplified by looking at basic physical and cellular processes. .Carbon dioxide, produced by thyroid function, protects the circulatory system in ways that give insight into many other processes.

Somehow, these two fetid streams converged: **Estrogen, like the unsaturated oils, lowered the amount of cholesterol in the blood,** and an excess of blood cholesterol was said to cause heart attacks. (And, more recently, the estrogenic effects of the seed oils are claimed to offer protection against cancer.)

NO cert un F.R. accélère vieill du cerveau

The ability to lower the cholesterol "risk factor" for heart attacks became a cultural icon, so that the contribution of estrogen and unsaturated oils to the pathologies of clotting could be ignored. Likewise, the contribution of unsaturated fats' lipid peroxidation to the development of atherosclerotic plaques was simply ignored. But one of estrogen's long established toxic effects, the reduction of tone in veins, was turned into something like a "negative risk factor": The relaxation of blood vessels would prevent high blood pressure and its consequences, in this new upside down paradigm. **This vein-dilating effect of estrogen has been seen to play a role in the development of varicose veins, in orthostatic hypotension, and in the formation of blood clots in the slow-moving blood in the large leg veins.**

When it was discovered that the endothelial relaxing factor was nitric oxide, a new drug business came into being. Nitroglycerine had been in use for decades to open blood vessels, and, ignoring the role of nitrite vasodilators in the acquired immunodeficiency syndrome, new drugs were developed to increase the production of nitric oxide. The estrogen industry began directing research toward the idea that estrogen works through nitric oxide to "improve" the function of blood vessels and the heart.

(Besides the argument based on "risk factors," many people cite the published observations that "women who take estrogen are healthier" than women who don't use it. But studies show that their "control groups" consisted of women who weren't as healthy to begin with.)

In the 1970s, after reading Szent-Gyorgyi's description of the antagonistic effect of progesterone and estrogen on the heart, I reviewed the studies that showed that progesterone protects against estrogen's clotting effect. I experimented with progesterone, showing that it increases the muscle tone in the walls of veins, which is very closely related to the effects Szent-Gyorgyi described in the heart. And progesterone opposes estrogen's ability to increase the amount of free fatty acids circulating in the blood.

More recently, it has been discovered that progesterone inhibits the expression of the enzyme nitric oxide synthase, while estrogen stimulates its expression. At the time of ovulation, when estrogen is high, a woman breathes out 50% more ***nitric oxide ("NO")*** than men do, but at other times, under the influence of increased progesterone and thyroid, and reduced estrogen, women exhale much less NO than men do. (Nitric oxide is a free radical, and it decomposes into other toxic compounds, including the free radical peroxynitrile, which damages cells, including the blood vessels. brain, and heart. Carbon dioxide tends to inhibit the production of peroxynitrile.)

If nitric oxide produced under the influence of estrogen were important in preventing cardiovascular disease, then men's larger production of nitric oxide would give them greater protection than women have.

From more realistic perspectives, nitric oxide is being considered as a cause of aging, especially brain aging. **Nitric oxide interacts with unsaturated fats to reduce oxygen use, damage mitochondria, and cause edema.**

I think we can begin to see that the various "heart protective" ideas that have been promoted to the public for fifty years are coming to a dead end, and that a new look at the fundamental problems involved in heart disease would be appropriate. Basic principles that make heart disease more understandable will also be useful for understanding **shock, edema, panic attacks, high altitude sickness, high blood pressure, kidney disease, some lung diseases, MS, multiple organ failure, and excitotoxicity or "programmed" cell death of the sort that causes degenerative nerve diseases and deterioration of other tissues.**

The research supporting this view is remarkably clear, but it isn't generally known because of the powerful propaganda coming from the drug and oil industries and their public servants.

Broda Barnes was right when he said that the "riddle of heart attacks" was solved when he demonstrated that hypothyroidism caused heart attacks, and that they were prevented by correcting hypothyroidism. He also observed that correcting hypothyroidism prevented the degenerative conditions (including heart disease) that so

often occur in diabetics. Since hypothyroidism and diabetes are far more frequent in women, who have fewer heart attacks than men, it is appropriate to wonder why women tolerate hypothyroidism better than men.

In hypothyroidism and diabetes, respiration is impaired, and lactic acid is formed even at rest, and relatively little carbon dioxide is produced. To compensate for the metabolic inefficiency of hypothyroidism, adrenalin and noradrenalin are secreted in very large amounts. Adrenalin causes free fatty acids to circulate at much higher levels, and the **lactic acid, adrenalin, and free fatty acids all stimulate hyperventilation.** The already deficient carbon dioxide is reduced even more, producing respiratory alkalosis. Free fatty acids, especially unsaturated fats, increase permeability of blood vessels, allowing proteins and fats to enter the endothelium and smooth muscle cells of the blood vessels. Lactic acid itself promotes an inflammatory state, and in combination with reduced CO2 and respiratory alkalosis, contributes to the hyponatremia (sodium deficiency) that is characteristic of hypothyroidism. This sodium deficiency and osmotic dilution causes cells to take up water, increasing their volume.

In hyperventilation, the heart's ability to work is decreased, and the work it has to do is increased, because peripheral resistance is increased, raising blood pressure. One component of peripheral resistance is the narrowing of the channels in blood vessels caused by endothelial swelling. In the heart, a similarly waterlogged state makes complete contraction and complete relaxation impossible.

Estrogen itself intensifies all of these changes of hypothyroidism, increasing perrmeability and edema, and decreasing the force of the heart-beat, impairing the diastolic relaxation. Besides its direct actions, and synergism with hypothyroidism, estrogen also chronically increases growth hormone, which causes **chronic exposure of the blood vessels to higher levels of free fatty acids (with a bias toward unsaturated fatty acids),** and promotes edema and vascular leakage. Hyperestrogenism, like hypothyroidism, tends to produce dilution of the body fluids, and is associated with increased bowel permeability, leading to endotoxemia; both dilution of the plasma and endotoxemia impair heart function.

Progesterone's effects are antagonistic to estrogen's:. Progesterone decreases the formation of nitric oxide, decreasing edema; it strengthens the heart beat, by improving venous return and increasing stroke volume, but at the same time it reduces peripheral resistance by relaxing arteries (by inhibiting calcium entry but also by other effects, and independently of the endothelium) and decreasing edematous swelling.

The effects of progesterone on the heart and blood vessels are paralleled by those of carbon dioxide: **Increased carbon dioxide increases perfusion of the heart muscle, increases its stroke volume, and reduces peripheral resistance.** The physical and chemical properties of carbon dioxide that I have written about previously include protective anti-excitatory and energy-sustaining functions that explain these effects. Since these effects have been known for many years, I think it is obvious that the obsessive interest in explaining these functions in terms of other molecules, such as nitric oxide, is motivated by the desire for new drugs, not by a desire to understand the physiology with which the researchers are pretending to deal.

Although women, because of estrogen's antithyroid actions, are much more likely to suffer from hypothyroidism than men are, until menopause they have much higher levels of progesterone than men do. The effects of hyperestrogenism and hypothyroidism, with lower carbon dioxide production, are offset by high levels of progesterone. After menopause, women begin to have heart attacks at a rapidly increasing rate.

During the years that men are beginning to have a considerable risk of heart attacks, with declining thyroid function indicated by lower T3, their testosterone and progesterone are declining, while their estrogen is rising. Men who have heart attacks have much higher levels of estrogen than men at the same age who haven't had a heart attack.

Whether the issue is free radical damage, vascular permeability with fat deposition, vascular

spasm, edema, decreased heart efficiency, or blood clotting, the effects of chronic estrogen exposure are counter-adaptive. **Progesterone, by opposing estrogen, is universally protective against vascular and heart disease.**

So far, the rule in most estrogen/progesterone research has been to devise experiments so that claims of benefit can be made for estrogen, with the expectation that they will meet an uncritical audience. In some studies, it's hard to tell whether idiocy or subterfuge is responsible for the way the experiment was designed and described, for example when synthetic chemicals with anti-progesterone activity are described as "progesterone." Since one estrogen-funded researcher who supposedly found progesterone to be ineffective as treatment for premenstrual syndrome practically admitted to me in conversation an intent to mislead, I think it is reasonable to discount idiocy as the explanation for the tremendous bias in published research. With the vastly increased resources in the estrogen industry, resulting from the product promotion "for the prevention of heart disease," I think we should expect the research fraud to become increasingly blatant.

Rather than being "heart protective," estrogen is highly heart-toxic, and it is this that makes its most important antagonist, progesterone, so important in protecting the heart and circulatory system.

REFERENCES

JAMA 1998 Aug 19;280(7):605-13. **Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.** Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E University of California, San Francisco 94143, USA. CONTEXT: Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials. OBJECTIVE: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease. DESIGN: Randomized, blinded, placebo-controlled secondary prevention trial. SETTING: Outpatient and community settings at 20 US clinical centers. PARTICIPANTS: A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. **Mean age was 66.7 years.** INTERVENTION: Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily **(n = 1380) or a placebo of identical appearance (n = 1383).** Follow-up averaged 4.1 years; **82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.** MAIN OUTCOME MEASURES: The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. **Secondary cardiovascular outcomes** included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered. RESULTS: Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect **occurred despite a net 11% lower low-density lipoprotein cholesterol level** and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each P<.001). Within the overall null effect, there was a statistically significant time trend, with more **CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5.** More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, **2.89**; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). **There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08;** 95% CI, 0.84-1.38). CONCLUSIONS: **During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events,** we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD

Am J Med 1982 Dec;73(6):872-81. **Serum estrogen levels in men with acute myocardial infarction.** Klaiber EL, Broverman DM, Haffajee CI, Hochman JS, Sacks GM, Dalen JE Serum estradiol and serum estrone levels were assessed in 29 men in 14 men in whom myocardial infarction was ruled out; in 12 men without apparent coronary heart disease but hospitalized in an intensive care unit; and in 28 men who were not hospitalized and who acted as control subjects. (The 12 men who were hospitalized but who did not have coronary heart disease were included to control for physical and emotional stress of a severe medical illness.) Ages ranged from 21 to 56 years. Age, height, and weight did not differ significantly among groups. Blood samples were obtained in the patient groups on each of the

first three days of hospitalization. The serum estrone level was significantly elevated in all four patient groups when compared with that in the control group. Estrone level, then, did not differentiate patients with and without coronary heart disease. **Serum estradiol levels were significantly elevated in the groups with myocardial infarction, unstable angina,** and in the group in whom myocardial infarction was ruled out. However, estradiol levels were not significantly elevated in the group in the intensive care unit without coronary heart disease when compared to the level in the normal control group. **Serum estradiol levels, then, were elevated in men with confirmed or suspected coronary heart disease** but were not elevated in men without coronary heart disease even under the stressful conditions found in an intensive care unit. Serum estradiol **levels were significantly and positively correlated (p less than 0.03) with serum total creatine phosphokinase** levels in the patients with myocardial infarction. The five patients with myocardial infarction who died within 10 days of admission had markedly elevated serum estradiol levels. The potential significance of these serum estradiol elevations is discussed in terms of estradiol's ability to enhance adrenergic neural activity and the resultant increase in myocardial oxygen demand.

JAMA 1978 Apr 3;239(14):1407-9. **Noncontraceptive estrogens and nonfatal myocardial infarction.** Jick H, Dinan B, Rothman KJ We obtained information on 107 women younger than 46 years discharged from a hospital with a diagnosis of acute myocardial infarction. In the series there were 17 women aged 39 to 45 years who were otherwise apparently healthy and had had a natural menopause, hysterectomy, or tubal ligation or whose spouse had had a vasectomy. Among them, nine (53%) were taking noncontraceptive estrogens just prior to admission. Among 34 control women, four (12%) were taking estrogens. The relative risk estimate, **comparing estrogen users with nonusers, is 7.5,** with 90% confidence limits of 2.4 and 24. All but one of the 17 ml subjects were cigarette smokers. While this illness is rare in most healthy young women, the risk in women older than about 38 years who both smoke and take estrogens appears to be substantial.

JAMA 1978 Apr 3;239(14):1403-6. **Oral contraceptives and nonfatal myocardial infarction.** Jick H, Dinan B, Rothman KJ We obtained information on 107 women younger than 46 years who were discharged from a hospital with a diagnosis of acute myocardial infarction. In the series 26 women were otherwise apparently healthy and potentially childbearing. Among these 26 women, 20 **(77%) were taking oral contraceptives just prior to admission, and one was taking conjugated estrogens. Among 59 control women, 14 (24%) were taking oral contraceptives and one was taking conjugated estrogens.** The relative risk estimate, comparing oral contraceptive users with nonusers, **is 14 with** 90% confidence limits of 5.5 and 37. All but two of the 26 women were cigarette smokers. While this illness is rare in most healthy young women, the risk in women older than about 37 years who both smoke and take oral contraceptive appears to be high.

M. Karmazyn, et al., **"Changes in coronary vascular resistance associated with prolonged hypoxia in isolated rat hearts: A possible role of prostaglandins,"** *Life Sciences 25,* 1991-1999, 1979. "if...hypoxic perfusion is prolonged, the initial dilatation passes off and an intense vasoconstriction results." **"The constriction could be prevented by progesterone but not by estradiol or testosterone."** "There is increasing evidence that angina pectoris and myocardiaol infarction may often be due to active caronary constriction." "Inhibitors of PG synthesis at high concentrations prevented or reversed the constriction." (Besides aspirin) "Chloroquine, procaine and propranolol can all behave as PG antagonists...." "The failure of estradiol or testosterone to have any effect and the complete prevention of the constriction by physiological levels of progesterone suggest that more attention should be paid to this last steroid." **"...hypoxia can cause coronary constriction and...the effect does not occur in young or progesterone-treated hearts...."**

Am J Epidemiol 1996 May 15;143(10):971-8. **Prior to use of estrogen replacement therapy, are users healthier than nonusers?** Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Observational studies have demonstrated that women who have used postmenopausal estrogen replacement therapy (ERT) are at reduced risk of coronary heart disease. The authors examined whether **premenopausal women who subsequently elected to use ERT during menopause had a better cardiovascular risk factor profile prior to use than did nonusers. A total of 541 premenopausal women had** their cardiovascular risk factors and psychosocial characteristics evaluated at study entry. After approximately 8 years, 355 women had become postmenopausal, and 157 women reported ERT use during the follow-up period (mean = 93.4 months). The authors compared the premenopausal characteristics of users with those of nonusers. Relative to nonusers, ERT users were better educated (63 vs. 81% with at least some college), and prior to the use of ERT had higher levels of high density lipoprotein (HDL) cholesterol (1.49 vs. 1.59 mmol/liter), HDL2 (0.50 vs. 0.57 mmol/liter), HDL3 (0.98 vs. 1.02 mmol/liter), leisure physical activity (5, 122 vs. 7,158 Kjoules), and alcohol intake (7.5 vs. 9.7 g/day), and lower levels of apolipoprotein B (0.97 vs. 0.90g/liter), systolic blood pressure (112.1 vs. 107.1 mmHg) and diastolic blood pressure (73.8 vs. 71.4 mmHg), weight (68.5 vs. 64.2 kg), and fasting insulin (9.10 vs. 7.66 microU/liter). **Prior to use of ERT, in comparison with nonusers, subsequent users reported on standardized questionnaires that they often exhibited Type A behavior, more aware of their feelings, motives, and symptoms, and had more symptoms of stress. Women who elect to use ERT have a better cardiovascular risk factor profile prior to the use of ERT than do women who subsequently do not use this treatment during the menopause, which supports the hypothesis that part of the apparent benefit associated with the use of ERT is due to preexisting characteristics of women who use ERT. This study underscores the widely recognized importance of randomized** clinical

trials to estimate the direct benefit of postmenopausal ERT for protecting women from cardiovascular disease.

"Effects of androgens on haemostasis," Winkler UH, Maturitas, 1996 Jul, 24:3, 147-55. **"Androgen deficiency is associated with an increased incidence of cardiovascular disease. There is evidence that thromboembolic disease as well as myocardial infarction in hypogonadic males are mediated by low baseline fibrinolytic activity.** Hypogonadism in males is associated with an enhancement of fibrinolytic inhibition via increased synthesis of the plasminogen activator inhibitor PAI 1."

M. Mabry White, et al., **"Estrogen, progesterone, and vascular reactivity: Potential cellular mechanisms,"** Endocrine Reviews 16(6), 739, 1995. "Female hormones are broadly recognized as affecting susceptibility to vascular disease...." Migraines, Raynaud's phenomena, primary pulmonary hypertension are mentioned as vascular disorders with a female predominance.

J. Boczkowski, et al., **"Induction of diaphragmatic nitric oxide synthase after endotoxin administration in rats; role on diaphragmatic contractile dysfunction,"** J. Clin. Invest. 98, 1550-1559, 1996. "We conclude that iNOS [inducible nitric oxide synthase] was induced..." by endotoxin.

Arch Int Pharmacodyn Ther 1986 May;281(1):57-65. **Effects of 17 beta-estradiol on the isolated rabbit heart.** Raddino R, Manca C, Poli E, Bolognesi R, Visioli O. We have studied the effects of 17 beta-estradiol on the left ventricular pressure and on the coronary perfusion pressure in isolated rabbit heart, in order to evaluate the action of this hormone on the myocardial contractility and on the coronary resistances. 17 beta-Estradiol has **induced a negative inotropic effect starting from a concentration of 10(-6) M and a vasodilation** starting from 10(-7) M when administered on a vasopressin-induced coronary spasm. These effects are not related to sex or to alpha-, beta-adrenergic, histaminergic, anaesthetic-like mechanisms, but seem to interfere with calcium transport.

Med Hypotheses 1997 Aug;49(2):183-5. **Coronary artery spasm: a hypothesis on prevention by progesterone.** Kanda I, Endo M. Department of Surgery, Heart Institute of Japan, Tokyo Women's Medical College, Japan. **The mechanism of coronary artery spasm has been hypothesized as follows: the dormant gene of the smooth muscle of the human coronary artery is identical or similar to the active gene of the smooth muscle of ductus arteriosus, but can be activated by estrogen. The activation could be preventable by progesterone. The prevention is due to the reduction of the number of estrogen receptors of the smooth muscle of the coronary artery.**

J. Bolanos, et al., **"Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes,"** J. Neurochem. 63, 910-916, 1994.

M. Cleeter, et al., **"Reversible inhibition of cytochrome C oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide,"** FEBS Lett. 345, 50-54, 1994.

Ann Thorac Surg 1999 Sep;68(3):925-30. **Coronary perfusate composition influences diastolic properties, myocardial water content, and histologic characteristics of the rat left ventricle.** Starr JP, Jia CX, Amirhamzeh MM, Rabkin DG, Hart JP, Hsu DT, Fisher PE, Szabolcs M, Spotnitz HM. "Recent studies found that edema, histology, and left **ventricular diastolic compliance** exhibit quantitative relationships in rats. Edema due to low osmolarity coronary perfusates increases myocardial water content and histologic edema score and **decreases left ventricular filling.** The present study examined effects of perfusate osmolarity and chemical composition on rat hearts." "Myocardial water content reflected perfusate osmolarity, being lowest in Stanford and University of Wisconsin solutions ($p<0.05$ versus other groups) and highest in dilute Plegisol ($p<0.05$). Left ventricular filling volumes were smallest in dilute Plegisol and Plegisol ($p<0.05$)." "Perfusate osmolarity determined myocardial water content and left ventricular filling volume. However, perfusate chemical composition influenced the histologic appearance of edema. Pathologic grading of edema can be influenced by factors other than osmolarity alone."

Progesterone inhibits inducible nitric oxide synthase gene expression and nitric oxide production in murine macrophages. Miller L; et al J Leukoc Biol, 59(3):442-50 1996 Mar. The purpose of this study was to determine whether the female hormones estradiol-17 beta (E2) and progesterone (P4) influence inducible nitric oxide synthase (iNOS) and the production of nitric oxide (NO) by interferon gamma (IFN-gamma) and lipopolysaccharide (LPS)-activated mouse macrophages. Treatment with P4 alone caused a time- and dose-dependent inhibition of NO production by macrophage cell lines (RAW 264.7, J774) and mouse bone marrow culture-derived macrophages as assessed by nitrite accumulation. RAW 264.7 cells transiently transfected with an iNOS gene promoter/luciferase reporter-gene construct that were stimulated with IFN-gamma/LPS in the presence of P4 displayed reduced luciferase activity and NO production. Analysis of RAW 264.7 cells by Northern blot hybridization revealed concurrent P4-mediated reduction in iNOS mRNA. These observations suggest that P4-mediated inhibition of NO may be an important gender-based difference within females and males that relates to macrophage-mediated host defense.

Testosterone relaxes rabbit coronary arteries and aorta. Yue P; Chatterjee K; Beale C; Poole-Wilson PA; Collins P Department of Cardiac Medicine, National Heart and Lung Institute, London, UK. Circulation, 1995 Feb 15, 91:4, 1154-60 **"Testosterone induces endothelium-independent relaxation in isolated rabbit coronary artery and aorta, which is neither mediated by prostaglandin I2 or cyclic GMP.** Potassium conductance and potassium channels but not ATP-sensitive potassium channels may be involved partially in the mechanism of testosterone-induced relaxation. The **in vitro relaxation is independent of sex and of a classic receptor.** The coronary artery is significantly more sensitive to relaxation by testosterone than the aorta. Testosterone is a more potent

relaxing agent of rabbit coronary artery than other testosterone analogues."

J. Nakamura, et al., **"Estrogen regulates vascular endothelial growth permeability factor expression in 7,12-dimethyl- benz(a)anthracene-induced rat mammary tumors,"** Endocrinology 137(12_, 5589-5596, 1996. ("...one mechanism by which estrogen acts as a mammary tumor promotor is by stimulating VEG/PF, leading to increased tumor angiogenesis and/or permeability of the microvessels to allow tumor cell migration.")

D. A. Barber, et al., **"Endothelin receptors are modulated in association with endogenous fluctuations in estrogen,"** Amer. J. of Physiology--Heart and Circulatory Physiology 40(5), H1999-H2006, 1996. ("...contractions to endothelin-1 but not endothelin-3 or sarafotoxin S6c were significantly **greater in coronary arterial rings from female comparred with male pigs...." "In addition, independent of endogenous estrogen status, coronary arteries from female pigs generate significantly greater contractions to endothelin-1 compared with male pigs. This phenomenon occurs at the level of smooth muscle and is not dependent on the endothelium or synthesis of nitric oide or prostaglandins."**

T. M. Chou, et al, **"Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo,"** Circulation 94(10), 2614-2619, 1996.

K. Sudhir, et al., **"Estrogen enhances basal nitric oxide release in the forearm vasculature in perimenopausal women,"** Hypertension 28(3), 330-334, 1996.

G. Sitzler, et al., **"Investigation of the negative inotropic effects of 17-beta-oestradiol in human isolated myocardial tissues,"** British J. of Pharmacology 119(1), 43-48, 1996.

S. M. Hyder, et al., **"Uterine expression of vascular endothelial growth factor is increased by estradiol and tamoxifen,"** Cancer Research 56(17), 3954-3960, 1996. ("These findings raise the possibility that estrogen and antiestrogen effects on uterine edema, proliferation, and tumor incidence may involve local increases in tissue VEGF production.")

N. Ferrara and T. Davis-Smyth, **"The biology of vascular endothelial growth factor,"** Endocrine Reviews 18(1), 4-19,? 1997. "...induces vasodilatation in vitro in a dose-dependent fashion and produces transient tachycardia, hypotension, and a decrease in cardiac output when injected intravenously in conscious...rats. Such effects appear to be caused by a **decrease in venous return, mediated primarily by endothelial cell-derived nitric oxide...."** "Recently, elevation of VEGF in the peritoneal fluid of patients with endometriosis has been reported.""...it has been suggested that VEGF up-regulation plays a pathogenic role in the **capillary hyperpermeability** that characterizes ovarian hyperstimulation syndrome as well as in the dysfunctional endothelium of preeclampsia."

B. Jilma, et al, **"Sex differences in concentrtions of exhaled nitric oxide and plasma nitrate,"** Life Sciences 58*6), 469-476, 1996. ("Nitric oxide is generally considered as an endogenous vasoprotective agent." "...men exhaled 50% more NO and had 99% higher (nitrate) NO3 levels than women."

Progesterone inhibits inducible nitric oxide synthase gene expression and nitric oxide production in murine macrophages. Miller L; et al J Leukoc Biol, 59(3):442-50 1996 Mar. "Treatment with P4 alone caused a time- and dose-dependent **inhibition of NO production** by macrophage cell lines (RAW 264.7, J774) and mouse bone marrow culture-derived macrophages as assessed by nitrite accumulation. RAW 264.7 cells transiently transfected with an iNOS gene promoter/luciferase reporter-gene construct that were stimulated with IFN-gamma/LPS in the presence of P4 displayed reduced luciferase activity and NO production. Analysis of RAW 264.7 cells by Northern blot hybridization revealed concurrent P4-mediated reduction in iNOS mRNA. These observations suggest that P4-mediated inhibition of NO may be an important gender-based difference within females and males that relates to macrophage-mediated host defense."

Int J Epidemiol 1990 Jun;19(2):297-302. **Relationship of menopausal status and sex hormones to serum lipids and blood pressure.** Wu ZY, Wu XK, Zhang YW. **"Conditional logistic regression analysis found that progesterone is a protective factor only and testosterone is one of the risk factors for hypertension."**

Pharmacol Biochem Behav 1990 Oct;37(2):325-7. **Steroid sex hormones and cardiovascular function in healthy males and females: a correlational study.** Lundberg U, Wallin L, Lindstedt G, Frankenhaeuser M Department of Psychiatry and Psychology, Karolinska Institutet, Sweden. "The relationship of serum estradiol and testosterone levels to systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) was examined in healthy nonsmoking males (n = 30) and females (n = 22), 30-50 years of age (mean age for men = 41.2, women = 39.9). Postmenopausal women and women taking oral contraceptives had been excluded. Testosterone levels in women were positively correlated with SBP, DBP and HR, after removing the effects of age and body mass. **Positive correlations were also found between estradiol and SBP and HR in women."**

Scand J Clin Lab Invest 1993 Jul;53(4):353-8. **Effects of ovarian stimulation on blood pressure and plasma catecholamine levels.** Tollan A, Oian P, Kjeldsen SE, Holst N, Eide I. **"After stimulation a positive correlation was observed between systolic blood pressure and arterial adrenaline (r = 0.73, p = 0.027), and between systolic blood pressure and the arterial-venous difference for adrenaline (r = 0.81, p = 0.007). The increased venous noradrenaline levels may be a reflex-mediated activation** of the sympathetic nervous tone due to a decrease in blood pressure, or may indicate reduced neuronal re-uptake of released noradrenaline. The mechanisms behind the **strong correlation between adrenaline and blood pressure are unclear, but may be induced by the supra-physiological oestradiol levels."**

J Mol Cell Cardiol 1986 Dec;18(12):1207-18. **Post-ischemic cardiac chamber stiffness and coronary**

vasomotion: the role of edema and effects of dextran. Vogel WM, Cerel AW, Apstein CS. "Contributions of edema to left ventricular (LV) chamber stiffness and coronary resistance after ischemia were studied in isolated buffer-perfused rabbit hearts, with constant LV chamber volume, subjected to 30 min global ischemia and 60 min reperfusion. During reperfusion hearts were perfused with standard buffer or with 3% dextran to increase oncotic pressure and decrease water content." "Coronary resistance in untreated ischemic hearts increased by 26% from 2.0 +/- 0.06 to 2.6 +/- 0.06 mmHg/ml/min after 60 min reperfusion. In treated hearts coronary resistance increased by 16% from 1.9 +/- 0.09 to 2.2 +/- 0.09 mm/Hg/ml/min (P less than 0.01 v. untreated ischemic). To determine whether the decrease in coronary **resistance with dextran could be ascribed to active vasodilation, dilator responses to 2 min hypoxia or 10(-4)M adenosine were tested in nonischemic and reperfused ischemic hearts. Dilator responses were stable in nonischemic hearts or hearts reperfused after 15 min ischemia but after 30 min ischemia the dilator response to hypoxia was reduced by 72% (P less than 0.025) and the dilator response to adenosine was eliminated (P less than 0.02). Thus the response to dextran was unlike that of a direct vasodilator. These data suggest that myocardial edema plays a significant role in maintaining increased ventricular chamber stiffness and coronary resistance during reperfusion after ischemia."**

Experientia 1980 Dec 15;36(12):1402-3. **Bilinear correlation between tissue water content and diastolic stiffness of the ventricular myocardium.** Pogatsa G. **In oedematous and dehydrated canine hearts a close bilinear correlation was demonstrated between myocardial water content and diastolic stiffness (characterized by the passive elastic modulus) with an optimal minimum of stiffness at normal myocardial water content.**

S Afr Med J 1975 Dec 27;49(55):2251-4. **Effect of natural oestrogens on blood pressure and weight in postmenopausal women.** Notelovitz M. "An investigation of the effect of conjugated oestorgens (USP) on the blood pressure and weight gain of postmenopausal women was undertaken. Fifty-one unselected women were treated for one year with cyclically administered conjugated oestrogen. Both the mean systolic and diastolic blood pressures of **those in the group increased, but only the diastolic was significantly elevated."** "The significance of the change in blood pressure is commented upon, and the recommendation that postmenopausal women on oestrogen replacement therapy should have their blood pressure measured every 6 months is made."

Am J Hypertens 1995 Mar;8(3):249-53. **Ambulatory blood pressure in mild hypertensive women taking oral contraceptives. A case-control study.** Narkiewicz K, Graniero GR, D'Este D, Mattarei M, Zonzin P, Palatini P. "Both daytime and nighttime systolic **blood pressure values were significantly higher in oral contraceptive users. There was an average 8.3 mm** Hg difference (95% confidence interval, 3.0 to 13.7 mm Hg; P = .003) for the daytime and 6.1 mm Hg difference (95% confidence interval, 0.4 to 11.8 mm Hg; P = .04) for the nighttime." "Our results support the opinion that alternative methods of contraception should be considered for hypertensive women in place of oral contraceptives."

Am J Surg Pathol 1995 Apr;19(4):454-62. **Reversible ischemic colitis in young women. Association with oral contraceptive use.** Deana DG, Dean PJ. ."Ischemic colitis, a condition of middle-aged to elderly patients, occurs uncommonly in younger persons." "Ten women (59%) were using low-dose estrogenic oral contraceptive agents, compared with the 1988 national average of 18.5% oral contraceptive users among females aged 15 to 44 years. **The calculated odds ratio yielded a greater than sixfold relative risk for the occurrence of ischemic colitis among oral contraceptive users.** In addition, four women not currently on hormonal contraceptive therapy had a past history of oral contraceptive use; the three remaining women were taking estrogen as replacement therapy after oophorectomy. In one patient, documented reversible ischemic colitis recurred on resumption of oral contraceptive use...." "...spontaneous ischemic colitis is a disorder found almost exclusively in women and is associated with the clinical use of exogenous estrogenic agents."

J Clin Endocrinol Metab 1993 Jun;76(6):1542-7. **Differential changes in serum concentrations of androgens and estrogens (in relation with cortisol) in postmenopausal women with acute illness.** Spratt DI, Longcope C, Cox PM, Bigos ST, Wilbur-Welling C. "We evaluated relationships between changes in serum levels of cortisol (F), androgens, estrogens, and gonadotropins in 20 postmenopausal women with acute critical illness to determine if changes in adrenal androgens and estrogens paralleled gonadal axis suppression or adrenal stimulation. **Two patterns of changes in sex steroids were observed. Admission serum levels of androstenedione (delta 4-A), estradiol, and estrone, like F, were increased compared to healthy controls (P < 0.0001). delta 4-A and estrone then decreased toward normal by day 5 in parallel with cortisol (r = 0.56 and 0.60).**" "The decreased serum T levels suggest inhibition of 17 beta-OH-dehydrogenase **and/or increased aromatization to estradiol. The marked increase in serum estrogen levels also suggests increased aromatization.** The absence of increases in DHEA and DHEA-S suggest enhanced activity of 3 beta-hydroxysteroid dehydrogenase and/or inhibition of C17,20-lyase activity of P-450c17.".

Since the first doctor noticed, hundreds of years ago, that the urine of a diabetic patient tasted sweet, it has been common to call the condition the sugar disease, or sugar diabetes, and since nothing was known about physiological chemistry, it was commonly believed that eating too much **sugar had to be the cause, since the ability of the body to convert the protein in tissues into sugar wasn't discovered until** 1848, by Claude Bernard (who realized that diabetics lost more sugar than they took in). Even though patients continued to pass sugar in their urine until they died, despite the elimination of sugar from their diet, medical policy required that they be restrained to keep them from eating sugar. That prescientific medical belief, that eating sugar causes diabetes, is still held by a very large number, probably the majority, of physicians.

Originally, diabetes was understood to be a wasting disease, but as it became common for doctors to measure glucose, obese people were often found to have hyperglycemia, so the name diabetes has been extended to them, as type 2 diabetes. High blood sugar is often seen along with high blood pressure and obesity in Cushing's syndrome, with excess cortisol, and these features are also used to define the newer metabolic syndrome.

Following the old reasoning about the sugar disease, the newer kind of obese diabetes is commonly blamed on eating too much sugar. Obesity, especially a fat waist, and all its associated health problems, are said by some doctors to be the result of eating too much sugar, especially fructose. (Starch is the only common carbohydrate that contains no fructose.) Obesity is associated not only with diabetes or insulin resistance, but also with atherosIcerosis and heart disease, high blood pressure, generalized inflammation, arthritis, depression, risk of dementia, and cancer.

There is general agreement about the problems commonly associated with obesity, but not about the causes or the way to prevent or cure obesity and the associated conditions.

In an earlier newsletter, I wrote about P. A. Piorry in Paris, in 1864, and Dr. William Budd in England, in 1867, who treated diabetes by adding a large amount of ordinary sugar, sucrose, to the patient's diet. Glucose was known to be the sugar appearing in the diabetics' urine, but sucrose consists of half glucose, and half fructose. In 1874, E. Kulz in Germany reported that diabetics could assimilate fructose better than glucose. In the next decades there were several more reports on the benefits of feeding fructose, including the reduction of glucose in the urine. With the discovery of insulin in 1922, fructose therapy was practically forgotten, until the 1950s when new manufacturing techniques began to make it economical to use.

Its use in diabetic diets became so popular that it became available in health food stores, and was also used in hospitals for intravenous feeding.

However, while fructose was becoming popular, the cholesterol theory of heart disease was being promoted. This was the theory that eating foods containing saturated fat and cholesterol caused heart disease. (My newsletter, Cholesterol, longevity, intelligence, and health, discussed the development of that theory.)

A Swedish physician and researcher, Uffe Ravnskov, has reviewed the medical arguments for the theory that lipids in the blood are the cause of atherosclerosis and heart disease, and shows that there has never been evidence of causality, something which some people, such as Broda Barnes, understood from the beginning. In the 1950s, an English professor, John Yudkin, didn't accept the idea that eating saturated fat was the cause of **high blood levels of triglycerides and cholesterol, but he didn't question the theory that lipids in the blood caused the cir**culatory disease. He argued that it was sugar, especially the fructose component of sucrose, rather than dietary fat that caused the high blood lipids seen in the affluent countries, and consequently the diseases. He was sure it was a specific chemical effect of the fructose, because he argued that the nutrients that were removed in refining white flour and white sugar were insignificant, in the whole diet.

Following the publication of Yudkin's books, and coinciding with increasing promotion of the health benefits of unsaturated vegetable oils, many people were converted to Yudkin's version of the lipid theory of heart disease, i.e., that the "bad lipids" in the blood are the result of eating sugar. This has grown into essentially a cult, in which sugar is believed to act like an intoxicant, forcing people to eat until they become obese, and develop the "metabolic syndrome," and "diabetes," and the many problems that derive from that.

The publicity campaign against "saturated fat" as an ally of cholesterol derived its support from the commercial promotion of the polyunsaturated seed oils as food for humans. Although the early investigators of vitamin E knew that the polyunsaturated oils could cause sterility, and others later found that their use in commercial animal foods could cause brain degeneration, there were a few biologists (mostly associated with George Burr) who believed that this type of fatty acid is an essential nutrient.

George and Mildred Burr had created what they claimed to be a disease in rats caused by the absence of linoleic or linolenic acid in their food. Although well known researchers had previously published evidence that animals on a fat free diet were healthy--even healthier than on a normal diet--Burr and his wife published their contradictory claim without bothering to discuss the conflicting evidence. I haven't seen any instance in which Burr or his followers ever mentioned the conflicting evidence. Although other biologists didn't accept Burr's claims, and several researchers subsequently published contrary results, he later became famous when the seed oil industry wanted scientific-seeming reasons for selling their product as an "essential" food. The fact that eating the polyunsaturated fats could cause the blood cholesterol level to decrease slightly was advertised as a health benefit. Later, when human trials showed that more people on the "heart healthy" diet died of heart disease and cancer, more conventional means of advertising were used instead of human tests.

Burr's experimental diet consisted of purified casein (milk protein) and purified sucrose, supplemented with a vitamin concentrate and some minerals. Several of the B vitamins weren't known at the time, and the mineral mixture lacked zinc, copper, manganese, molybdenum, and selenium. More of the essential nutrients were unknown in his time than in Yudkin's, so his failure to consider the possibility of other nutritional deficiencies affecting health is more understandable.

In 1933, Burr observed that his fat-deficient rats consumed oxygen at an extremely high rate, and even then, the thought didn't occur to him that other nutritional deficiencies might have been involved in the condition he described. Ordinarily, the need for vitamins and minerals corresponds to the rate at which calories are being burned, the metabolic rate. Burr recalled that the rats on the fat free diet drank more water, and he reasoned that the absence of linoleic or linolenic acid in their skin was allowing water vapor to escape at a high rate. He didn't explain why the saturated fats the rats were synthesizing from sugar didn't serve at least as well as a "vapor barrier"; they are more effective at water-proofing than unsaturated fats, because of their greater hydrophobicity. The condensed and cross-linked keratin protein in skin cells is the main reason for the skin's relatively low permeability. When an animal is burning calories at a higher rate, its sweat glands are more actively maintaining a normal body temperature, cooling by evaporation; the amount of water evaporated is an approximate measure of metabolic rate, and of thyroid function.

In 1936, a man in Burr's lab, William Brown, agreed to eat a similar diet for six months, to see whether the "essential fatty acid deficiency"

affected humans as it did rats.

The diet was very similar to the rats', with a large part of the daily 2500 calories being provided at hourly intervals during the day by sugar syrup (flavored with citric acid and anise oil), protein from 4 quarts of special fat-free skimmed milk, a quart of which was made into cottage cheese, the juice of half an orange, and a "biscuit" made with potato starch, baking powder, mineral oil, and salt, with iron, viosterol (vitamin D), and carotene supplemented.

Brown had suffered from weekly migraine headaches since childhood, and his blood pressure was a little high when he began the diet. After six weeks on the diet, his migraines stopped, and never returned. His plasma inorganic phosphorus declined slightly during the experiment (3.43 mg./100 cc. of plasma and 2.64 on the diet, and after six months on a normal diet 4.2 mg.%), and his total serum proteins increased from 6.98 gm.% to 8.06 gm.% on the experimental diet. His leucocyte count was lower on the high sugar diet, but he didn't experience colds or other sickness. On a normal diet, his systolic blood pressure varied from 140 to 150 mm. of mercury, the diastolic, 95 to 100. After a few months on the sugar and milk diet, his blood pressure had lowered to about 130 over 85 to 88. Several months after he returned to a normal diet, his blood pressure rose to the previous level.

On a normal diet, his weight was 152 pounds, and his metabolic rate was from 9% to 12% below normal, but after six months on the diet it had increased to 2% below normal. After three months on the sugar and milk diet, his weight leveled off at 138 pounds. After being on the diet, when he ate 2000 calories of sugar and milk within two hours, his respiratory quotient would exceed 1.0, but on his normal diet his maximum respiratory quotient following those foods was less than 1.0.

The effect of diabetes is to keep the respiratory quotient low, since a respiratory quotient of one corresponds to the oxidation of pure carbohydrate, and extreme diabetics oxidize fat in preference to carbohydrate, and may have a quotient just a little above 0.7. The results of Brown's and Burr's experiments could be interpreted to mean that the polyunsaturated fats not only lower the metabolic rate, but especially interfere with the metabolism of sugars. In other words, they suggest that the normal diet is diabetogenic.

During the six months of the experiment, the unsaturation of Brown's serum lipids decreased. The authors reported that "There was no essential change in the serum cholesterol as a result of the change in diet." However, in November and December, two months before the experiment began, it had been 252 mg.% in two measurements. At the beginning of the test, it was 298, two weeks later, 228, and four months later, 206 mg%. The total quantity of lipids in his blood didn't seem to change much, since the triglycerides increased as the cholesterol decreased.

By the time of Brown's experiment, other researchers had demonstrated that the cholesterol level was increased in hypothyroidism, and decreased as thyroid function, and oxygen consumption, increased. If Burr's team had been reading the medical literature, they would have understood the relation between Brown's increased metabolic rate and decreased cholesterol level. But they did record the facts, which is valuable.

The authors wrote that "The most interesting subjective effect of the 'fat-free' regimen was the definite disappearance of a feeling of fatigue at the end of the day's work."

A lowered metabolic rate and energy production is a common feature of aging and most degenerative diseases. From the beginning of an animal's life, sugars are the primary source of energy, and with maturation and aging there is a shift toward replacing sugar oxidation with fat oxidation. Old people are able to metabolize fat at the same rate as younger people, but their overall metabolic rate is lower, because they are unable to oxidize sugar at the same high rate as young people. Fat people have a similar selectively reduced ability to oxidize sugar.

Stress and starvation lead to a relative reliance on the fats stored in the tissues, and the mobilization of these as circulating free fatty acids contributes to a slowing of metabolism and a shift away from the use of glucose for energy. This is adaptive in the short term, since relatively little glucose is stored in the tissues (as glycogen), and the proteins making up the body would be rapidly consumed for energy, if it were not for the reduced energy demands resulting from the effects of the free fatty acids.

One of the points at which fatty acids suppress the use of glucose is at the point at which it is converted into fructose, in the process of glycolysis. When fructose is available, it can by-pass this barrier to the use of glucose, and continue to provide pyruvic acid for continuing oxidative metabolism, and if the mitochondria themselves aren't providing sufficient energy, it can leave the cell as lactate, allowing continuing glycolytic energy production. In the brain, this can sustain life in an emergency.

Many people lately have been told, as part of a campaign to explain the high incidence of fatty liver degeneration in the US, supposedly resulting from eating too much sugar, that fructose can be metabolized only by the liver. The liver does have the highest capacity for metabolizing fructose, but the other organs do metabolize it.

If fructose can by-pass the fatty acids' inhibition of glucose metabolism, to be oxidized when glucose can't, and if the metabolism of diabetes involves the oxidation of fatty acids instead of glucose, then we would expect there to be less than the normal amount of fructose in the serum of diabetics, although their defining trait is the presence of an increased amount of glucose. According to Osuagwu and Madumere (2008), that is the case. If a fructose deficiency exists in diabetes, then it is appropriate to supplement it in the diet.

Besides being one of the forms of sugar involved in ordinary energy production, interchangeable with glucose, fructose has some special functions, that aren't as well performed by glucose. It is the main sugar involved in reproduction, in the seminal fluid and intrauterine fluid, and in the developing fetus. After these crucial stages of life are past, glucose becomes the primary molecular source of energy, except when the system is under stress. It has been suggested (Jauniaux, et al., 2005) that the predominance of fructose rather than glucose in the embryo's environment helps to maintain ATP and the oxidative state (cellular redox potential) during development in the low-oxygen environment. The placenta turns glucose from the mother's blood into fructose, and the fructose in the mother's blood can pass through into the fetus, and although glucose can move back from the fetus into the mother's blood, fructose is unable to move in that direction, so a high concentration is maintained in the fluids around the fetus.

The control of the redox potential is sometimes called the "redox signalling system," since it coherently affects all processes and conditions in the cell, including pH and hydrophobicity. For example, when a cell prepares to divide, the balance shifts strongly away from the oxidative condition, with increases in the ratios of NADH to NAD+, of GSH to GSSG, and of lactate to pyruvate. These same shifts occur during most kinds of stress.

In natural stress, decreased availability of oxygen or nutrients is often the key problem, and many poisons can produce similar interference with

energy production, for example cyanide or carbon monoxide, which block the use of oxygen, or ethanol, which inhibits the oxidation of sugars, fats, and amino acids (Shelmet, et al., 1988).

When oxygen isn't constantly removing electrons from cells (being chemically reduced by them) those electrons will react elsewhere, creating free radicals (including activated oxygen) and reduced iron, that will create inappropriate chemical reactions (Niknahad, et al., 1995; MacAllister, et al., 2011).

Stresses and poisons of many different types, interfering with the normal flow of electrons to oxygen, produce large amounts of free radicals, which can spread structural and chemical damage, involving all systems of the cell. Ethyl alcohol is a common potentially toxic substance that can have this effect, causing oxidative damage by allowing an excess of electrons to accumulate in the cell, shifting the cells' balance away from the stable oxidized state.

Fructose has been known for many years to accelerate the oxidation of ethanol (by about 80%). Oxygen consumption in the presence of ethanol is increased by fructose more than by glucose (Thieden and Lundquist, 1967). Besides removing the alcohol from the body more quickly, it prevents the oxidative damage, by maintaining or restoring the cell's redox balance, the relatively oxidized state of the NADH/NAD+, lactate/pyruvate, and GSH/GSSH systems. Although glucose has this stabilizing, pro-oxidative function in many situations, this is a general feature of fructose, sometimes allowing it to have the opposite effect of glucose on the cell's redox state. It seems to be largely this generalized shift of the cell's redox state towards oxidation that is behind the ability of a small amount of fructose to catalyze the more rapid oxidation of a large amount of glucose.

Besides protecting against the reductive stresses, fructose can also protect against the oxidative stress of increased hydrogen peroxide (Spasojevic, et al., 2009). Its metabolite, fructose 1,6-bisphosphate, is even more effective as an antioxidant.

Keeping the metabolic rate high has many benefits, including the rapid renewal of cells and their components, such as cholesterol and other lipids, and proteins, which are always susceptible to damage from oxidants, but the high metabolic rate also tends to keep the redox system in the proper balance, reducing the rate of oxidative damage.

Endotoxin absorbed from the intestine is one of the ubiquitous stresses that tends to cause free radical damage. Fructose, probably more than glucose, is protective against damage from endotoxin.

Many stressors cause capillary leakage, allowing albumin and other blood components to enter extracellular spaces or to be lost in the urine, and this is a feature of diabetes, obesity, and a variety of inflammatory and degenerative diseases including Alzheimer's disease (Szekanecz and Koch, 2008; Ujiie, et al., 2003). Although the mechanism isn't understood, fructose supports capillary integrity; fructose feeding for 4 and 8 weeks caused a 56% and 51% reduction in capillary leakage, respectively (Chakir, et al., 1998; Plante, et al., 2003).

The ability of the mitochondria to oxidize pyruvic acid and glucose is characteristically lost to some degree in cancer. When this oxidation fails, the disturbed redox balance of the cell will usually lead to the cell's death, but if it can survive, this balance favors growth and cell division, rather than differentiated function. This was Otto Warburg's discovery, that was rejected by official medicine for 75 years.

Cancer researchers have become interested in this enzyme system that controls the oxidation of pyruvic acid (and thus sugar) by the mitochondria, since these enzymes are crucially defective in cancer cells (and also in diabetes). The chemical DCA, dichloroacetate, is effective against a variety of cancers, and it acts by reactivating the enzymes that oxidize pyruvic acid. Thyroid hormone, insulin, and fructose also activate these enzymes. These are the enzymes that are inactivated by excessive exposure to fatty acids, and that are involved in the progressive replacement of sugar oxidation by fat oxidation, during stress and aging, and in degenerative diseases; for example, a process that inactivates the energy-producing pyruvate dehydrogenase in Alzheimer's disease has been identified (Ishiguro, 1998). Niacinamide, by lowering free fatty acids and regulating the redox system, supporting sugar oxidation, is useful in the whole spectrum of metabolic degenerative diseases.

A few times in the last 80 years, people (starting with Nasonov) have recognized that the hydrophobicity of a cell changes with its degree of excitation, and with its energy level. Recently, even in non-living physical-chemical systems, hydrophobicity and redox potential have been seen to vary together and to influence each other. Recent work shows how the oxidation of fatty acids contributes to the dissolution of mitochondria (Macchioni, et al., 2010). At first glance it might seem odd that the presence of fatty material could reduce the "fat loving" (lipophilic, equivalent to hydrophobic) property of a cell, but the fat used as fuel is in the form of fatty acids, which are soap-like, and spontaneously introduce "wetness" into the relatively water-resistant cell substance. The presence of fatty acids, impairing the last oxidative stage of respiration, increases the tendency of the mitochondrion to release its cytochrome c into the cell in a reduced form, leading to the apoptotic death of the cell. The oxidized form of the cytochrome is more hydrophobic, and stable.

Burr didn't understand that it was his rats' high sugar diet, freed of the anti-oxidative unsaturated fatty acids, that caused their extremely high metabolic rate, but since that time many experiments have made it clear that it is specifically the fructose component of sucrose that is protective against the antimetabolic fats.

Although Brown, et al., weren't focusing on the biological effects of sugar, their results are important in the history of sugar research because their work was done before the culture had been influenced by the development of the lipid theory of heart disease, and the later idea that fructose is responsible for increasing the blood lipids.

In 1963 and 1964, experiments (Carroll, 1964) showed that the effects of glucose and fructose were radically affected by the type of fat in the diet. Although 0.6% of calories as polyunsaturated fat prevents the appearance of the Mead acid (which is considered to indicate a deficiency of essential fats) the "high fructose" diets consistently add 10% or more corn oil or other highly unsaturated fat to the diet. These large quantities of PUFA aren't necessary to prevent a deficiency, but they are needed to obscure the beneficial effects of fructose.

Many studies have found that sucrose is less fattening than starch or glucose, that is, that more calories can be consumed without gaining weight. During exercise, the addition of fructose to glucose increases the oxidation of carbohydrate by about 50% (Jentjens and Jeukendrup, 2005). In another experiment, rats were fed either sucrose or Coca-Cola and Purina chow, and were allowed to eat as much as they wanted (Bukowiecki, et al, 1983). They consumed 50% more calories without gaining extra weight, relative to the standard diet. Ruzzin, et al. (2005) observed rats given a

10.5% or 35% sucrose solution, or water, and observed that the sucrose increased their energy consumption by about 15% without increasing weight gain. Macor, et al. (1990) found that glucose caused a smaller increase in metabolic rate in obese people than in normal weight people, but that fructose increased their metabolic rate as much as it did that of the normal weight people. Tappy, et al. (1993) saw a similar increase in heat production in obese people, relative to the effect of glucose. Brundin, et al. (1993) compared the effects of glucose and fructose in healthy people, and saw a greater oxygen consumption with fructose, and also an increase in the temperature of the blood, and a greater increase in carbon dioxide production.

These metabolic effects have led several groups to recommend the use of fructose for treating shock, the stress of surgery, or infection (e.g., Adolph, et al., 1995).

The commonly recommended alternative to sugar in the diet is starch, but many studies show that it produces all of the effects that are commonly ascribed to sucrose and fructose, for example hyperglycemia (Villaume, et al., 1984) and increased weight gain. The addition of fructose to glucose "can markedly reduce hyperglycemia during intraportal glucose infusion by increasing net hepatic glucose uptake even when insulin secretion is compromised" (Shiota, et al., 2005). "Fructose appears most effective in those normal individuals who have the poorest glucose tolerance" (Moore, et al., 2000).

Lipid peroxidation is involved in the degenerative diseases, and many publications argue that fructose increases it, despite the fact that it can increase the production of uric acid, which is a major component of our endogenous antioxidant system (e.g., Waring, et al., 2003). When rats were fed for 8 weeks on a diet with 18% fructose and 11% saturated fatty acids, the content of polyunsatured fats in the blood decreased, as they had in the Brown, et al., experiment, and their total antioxidant status was increased (Girard, et al., 2005). When stroke-prone spontaneously hypertensive rats were given 60% fructose, superoxide dismutase in their liver was increased, and the authors suggest that this "may constitute an early protective mechanism" (Brosnan and Carkner, 2008). When people were given a 300 calorie drink containing glucose, or fructose, or orange juice, those receiving the glucose had a large increase in oxidative and inflammatory stress (reactive oxygen species, and NF-kappaB binding), and those changes were absent in those receiving the fructose or orange juice (Ghanim, et al., 2007).

One of the observations in Brown, et al., was that the level of phosphate in the serum decreased during the experimental diet. Several later studies show that fructose increases the excretion of phosphate in the urine, while decreasing the level in the serum. However, a common opinion is that it's only the phosphorylation of fructose, increasing the amount in cells, that causes the decrease in the serum; that could account for the momentary drop in serum phosphate during a fructose load, but--since there is only so much phosphate that can be bound to intracellular fructose--it can't account for the chronic depression of the serum phosphate on a continuing diet of fructose or sucrose.

There are many reasons to think that a slight reduction of serum phosphate would be beneficial. It has been suggested that eating fruit is protective against prostate cancer, by lowering serum phosphate (Kapur, 2000). The aging suppressing gene discovered in 1997, named after the Greek life-promoting goddess Klotho, suppresses the reabsorption of phosphate by the kidney (which is also a function of the parathyroid hormone), and inhibits the formation of the activated form of vitamin D, opposing the effect of the parathyroid hormone. In the absence of the gene, serum phosphate is high, and the animal ages and dies prematurely. In humans, in recent years a very close association has been has been documented between increased phosphate levels, within the normal range, and increased risk of cardiovascular disease. Serum phosphate is increased in people with osteoporosis (Gallagher, et al., 1980), and various treatments that lower serum phosphate improve bone mineralization, with the retention of calcium phosphate (Ma and Fu, 2010; Batista, et al., 2010; Kelly, et al., 1967; Parfitt, 1965; Kim, et al., 2003).

At high altitude, or when taking a carbonic anhydrase inhibitor, there is more carbon dioxide in the blood, and the serum phosphate is lower; sucrose and fructose increase the respiratory quotient and carbon dioxide production, and this is probably a factor in lowering the serum phosphate.

Fructose affects the body's ability to retain other nutrients, including magnesium, copper, calcium, and other minerals. Comparing diets with 20% of the calories from fructose or from cornstarch, Holbrook, et al. (1989) concluded "The results indicate that dietary fructose enhances mineral balance." Ordinarily, things (such as thyroid and vitamin D) which improve the retention of magnesium and other nutrients are considered good, but the fructose mythology allows researchers to conclude, after finding an increased magnesium balance, with either 4% or 20% of energy from fructose (compared to cornstarch, bread, and rice), "that dietary fructose adversely affects macromineral homeostasis in humans." (Milne and Nielsen, 2000).

Another study compared the effects of a diet with plain water, or water containing 13% glucose, or sucrose, or fructose, or high fructose corn syrup on the properties of rats' bones: Bone mineral density and mineral content, and bone strength, and mineral balance. The largest differences were between animals drinking the glucose and the fructose solutions. The rats getting the glucose had reduced phosphorus in their bones, and more calcium in their urine, than the rats that got fructose. "The results suggested that glucose rather than fructose exerted more deleterious effects on mineral balance and bone" (Tsanzi, et al., 2008).

An older experiment compared two groups with an otherwise well balanced diet, lacking vitamin D, containing either 68% starch or 68% sucrose. A third group got the starch diet, but with added vitamin D. The rats on the vitamin D deficient starch diet had very low levels of calcium in their blood, and the calcium content of their bones was low, exactly what is expected with the vitamin D deficiency. However, the rats on the sucrose diet, also vitamin D deficient, had normal levels of calcium in their blood. The sucrose, unlike the starch, maintained claim homeostasis. A radioactive calcium tracer showed normal uptake by the bone, and also apparently normal bone development, although their bones were lighter than those receiving vitamin D.

People have told me that when they looked for articles on fructose in PubMed they couldn't find anything except articles about its bad effects. There are two reasons for that. PubMed, like the earlier Index Medicus, represents the material in the National Library of Medicine, and is a medical, rather than a scientific, database, and there is a large amount of important research that it ignores. And because of the authoritarian and conformist nature of the medical profession, when a researcher observes something that is contrary to majority opinion, the title of the publication is unlikely to focus on that. In too many articles in medical journals, the title and conclusions positively misrepresent the data reported in the article.

When the idea of "glycemic index" was being popularized by dietitians, it was already known that starch, consisting of chains of glucose molecules, had a much higher index than fructose and sucrose. The more rapid appearance of glucose in the blood stimulates more insulin, and insulin stimulates fat synthesis, when there is more glucose than can be oxidized immediately. If starch or glucose is eaten at the same time as polyunsaturated fats, which inhibit its oxidation, it will produce more fat. Many animal experiments show this, even when they are intending to

show the dangers of fructose and sucrose.

For example (Thresher, et al., 2000), rats were fed diets with 68% carbohydrate, 12% fat (corn oil), and 20% protein. In one group the carbohydrate was starch (cornstarch and maltodextrin, with a glucose equivalence of 10%), and in other groups it was either 68% sucrose, or 34% fructose and 34% glucose, or 34% fructose and 34% starch. (An interesting oddity, fasting triglycerides were highest in the fructose+starch group.)

The weight of their fat pads (epididymal, retroperitoneal, and mesenteric) was greatest in the fructose+starch group, and least in the sucrose group. The starch group's fat was intermediate in weight between those of the sucrose and the fructose+glucose groups.

At the beginning of the experimental diet, the average weight of the animals was 213.1 grams. After five weeks, the animals in the fructose+glucose group gained 164 grams, those in the sucrose group gained 177 grams, and those in the starch group gained 199.2 grams. The animals ate as much of the diet as they wanted, and those in the sucrose group ate the least.

The purpose of their study was to see whether fructose causes "glucose intolerance" and "insulin resistance." Since insulin stimulates appetite (Chance, et al, 1986; Dulloo and Girardier, 1989; Czech, 1988; DiBattista, 1983; Sonoda, 1983; Godbole and York, 1978), and fat synthesis, the reduced food consumption and reduced weight gain show that fructose was protecting against these potentially harmful effects of insulin.

Much of the current concern about the dangers of fructose is focussed on the cornstarch-derived high fructose corn syrup, HFCS. Many studies assume that its composition is nearly all fructose and glucose. However, Wahjudi, et al. (2010) analyzed samples of it before and after hydrolyzing it in acid, to break down other carbohydrates present in it. They found that the carbohydrate content was several times higher than the listed values. "The underestimation of carbohydrate content in beverages may be a contributing factor in the development of obesity in children," and it's especially interesting that so much of it is present in the form of starch-like materials.

Many people are claiming that fructose consumption has increased greatly in the last 30 or 40 years, and that this is responsible for the epidemic of obesity and diabetes. According to the USDA Economic Research Service, the 2007 calorie consumption as flour and cereal products increased 3% from 1970, while added sugar calories decreased 1%. Calories from meats, eggs, and nuts decreased 4%, from dairy foods decreased 3%, and calories from added fats increased 7%. The percentage of calories from fruits and vegetables stayed the same. The average person consumed 603 calories per day more in 2007 than in 1970. If changes in the national diet are responsible for the increase of obesity, diabetes, and the diseases associated with them, then it would seem that the increased consumption of fat and starch is responsible, and that would be consistent with the known effects of starches and polyunsaturated fats.

In monkeys living in the wild, when their diet is mainly fruit, their cortisol is low, and it rises when they eat a diet with less sugar (Behie, et al., 2010). Sucrose consumption lowers ACTH, the main pituitary stress hormone (Klement, et al., 2009; Ulrich-Lai, et al., 2007), and stress promotes increased sugar and fat consumption (Pecoraro, et al., 2004). If animals' adrenal glands are removed, so that they lack the adrenal steroids, they choose to consume more sucrose (Laugero, et al., 2001). Stress seems to be perceived as a need for sugar. In the absence of sucrose, satisfying this need with starch and fat is more likely to lead to obesity.

The glucocorticoid hormones inhibit the metabolism of sugar. Sugar is essential for brain development and maintenance. The effects of environmental stimulation and deprivation-stress can be detected in the thickness of the brain cortex in as little as 4 days in growing rats (Diamond, et al., 1976). These effects can persist through a lifetime, and are even passed on transgenerationally. Experimental evidence shows that polyunsaturated (omega-3) fats retard fetal brain development, and that sugar promotes it. These facts argue against some of the currently popular ideas of the evolution of the human brain based on ancestral diets of fish or meat, which only matters as far as those anthropological theories are used to argue against fruits and other sugars in the present diet.

Honey has been used therapeutically for thousands of years, and recently there has been some research documenting a variety of uses, including treatment of ulcers and colitis, and other inflammatory conditions. Obesity increases mediators of inflammation, including the C-reactive protein (CRP) and homocysteine. Honey, which contains free fructose and free glucose, lowers CRP and homocysteine, as well as triglycerides, glucose, and cholesterol, while it increased insulin more than sucrose did (Al-Waili, 2004). Hypoglycemia intensifies inflammatory reactions, and insulin can reduce inflammation if sugar is available. Obesity, like diabetes, seems to involve a cellular energy deficiency, resulting from the inability to metabolize sugar.

Sucrose (and sometimes honey) is increasingly being used to reduce pain in newborns, for minor things such as injections (Guala, et al., 2001; Okan, et al., 2007; Anand, et al., 2005; Schoen and Fischell, 1991). It's also effective in adults. It acts by influencing a variety of nerve systems, and also reduces stress. Insulin is probably involved in sugar analgesia, as it is in inflammation, since it promotes entry of endorphins into the brain (Witt, et al., 2000).

An extracellular phosphorylated fructose metabolite, diphosphoglycerate, has an essential regulatory effect in the blood; another fructose metabolite, fructose diphosphate, can reduce mast cell histamine release and protect against oxidative and hypoxic injury and endotoxic shock, and it reduces the expression of the inflammation mediators TNF-alpha, IL-6, nitric oxide synthase, and the activation of NF-kappaB, among other protective effects, and its therapeutic value is known, but its relation to dietary sugars hasn't been investigated.

A daily diet that includes two quarts of milk and a quart of orange juice provides enough fructose and other sugars for general resistance to stress, but larger amounts of fruit juice, honey, or other sugars can protect against increased stress, and can reverse some of the established degenerative conditions.

Refined granulated sugar is extremely pure, but it lacks all of the essential nutrients, so it should be considered as a temporary therapeutic material, or as an occasional substitute when good fruit isn't available, or when available honey is allergenic.

Ray Peat's Newsletter

Love of power, operating through greed and through personal ambition, was the cause of all these evils. Thucydides

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X-rays, estrogen, and the brain

Even a single set of dental x-rays causes permanent systemic damage.

MRI (magnetic resonance imaging) and ultrasound imaging are much safer than x-rays and can provide better images of tissues, and can also provide detailed information about tissue functions and metabolism.

Diagnostic x-rays for dentistry, for measuring bone density, for mammography, for examining the brain, lungs, and heart, for "virtual colonoscopies," for shopping mall whole-body scans, should be abandoned immediately.

Their continued use is based partly on their profitability, partly on ignorance, and partly on the fear of legal liability for the death and disability already inflicted, if the truth is admitted.

The US Public Health Service has become deeply involved in scientific malfeasance over the last half century, and can be expected to marshal its minions to defend the present practices. Only public awareness can stop the radiological abuses.

The excitation of electrons in the tissues by radiation has catalytic effects that produce long-lasting changes in biological functions that are more important than any immediate genetic mutations.

Activation of phospholipase by radiation releases arachidonic acid and DHA, which act as biological signals. One enzyme activated by the arachidonic acid signals is estrogen synthetase. An early effect of irradiation is the stimulation of cell division, and this action is prolonged by the release of free unsaturated fatty acids and the formation of estrogen.

Chronic inflammatory changes, fibrosis, and amyloidosis are produced by ionizing radiation, even when the increased incidence of cancer or heart attacks is relatively small. Mental retardation, birth defects, senile dementia, immunodeficiency and the degenerative amyloidoses must now be taken into account in assessing the costs of radiation exposure.

The changes produced by high energy radiation overlap with those produced by excess polyunsaturated fats, excess serotonin, and excess estrogen.

Antioxidant, antiinflammatory, and antiestrogenic substances are protective against radiation damage. Aspirin, vitamin E, progesterone, saturated fats and thyroid have these functions.

For a century, science has been barbarized by greed. Early insights into the subtle electronic nature of life have been suppressed, allowing a crude mechanical concept of biochemistry to justify medical, military, and industrial practices that were convenient and profitable.

The observations of Gurwitsch, Crile, Tromp, Bernal, Barnothy, Szent-Gyorgyi, and others were disregarded, because they would have required science to confront the phenomenon of life with respect and humility, postponing the technological bio-engineering approach to organisms, in favor of caution and a recognition of the profundity of our ignorance.

Simplicity is nice, except when a simple model is claimed to accurately represent the complex reality. The 20th century saw the take-over of science by reductionism, and--not coincidentally--by the Corporate State. The field of biophysics in general, and radiation biology in particular, developed under the most extreme economic and political pressures, producing some dangerous distortions and delusions.

In the earliest years of the twentieth century, a few people like Thomas Edison had rejected the medical use of x-rays, because they had seen the rays' terrible effects on the body. But by the 1920s the US medical establishment was claiming that radiation was not only an essential diagnostic tool, but that it was the best way to treat more than eighty different conditions.

By the middle of the century, there were two views of the way that ionizing radiation such as the x-ray affects the body. One was that it accelerates the aging process, causing the degenerative diseases to occur at an earlier age. The other view was that it caused random mutations of the genes. (Although some people held that somatic mutations caused aging, there just wasn't much

interest in the scientific establishment in pursuing the question of aging.)

After 1945 the influence of the medical establishment coalesced with that of the developing military industrial atomic energy clique, to argue that ionizing radiation's "beneficial effects" far outweighed the trivial risks that large doses could produce. This medical-military culture found it useful to argue that there was a threshold for the harmful effects of radiation, and that below that dose, radiation had no harmful effect at all. That threshold dose was often considered to be the dose that caused radiation sickness to develop within a few days following exposure, in a way analogous to a sunburn that develops several hours after exposure to the sun. There was often an assumption that the threshold for mutation of genes was quite high, in the vicinity of the dose that produced radiation burns, but the outstanding thing about medical opinion regarding radiation's harmful effects was its fundamental optimism--if a treatment made you feel better for a couple of weeks, then it was unquestionably good for your health.

If anyone suggested that caution was appropriate in the absence of long-term evidence, that person was a danger to the livelihood of physicians and a threat to national security. Literally; that was the tone of the scientific-political culture. Even someone as famous as Linus Pauling was ostracized for saying that it was dangerous to test atomic bombs in the air. A few years ago, one of the Atomic Energy Commission's chief apologists for radioactive fallout in the 1950s, John Gofman, described his behavior at that time as simply stupid. Contemporary observers who didn't have a financial stake in radiation would have emphatically agreed with that assessment of his behavior, though at that time they assumed that he was dishonest rather than stupid. Although he still thinks nuclear weapons are good, he has done a great amount of good in the last 35 years by his careful studies of the harmful effects of radiation. But government and industry, and even some of his academic colleagues have done their best to destroy his reputation. Sternglass, Tamplin, Stewart, MacMahon, Mangano, and a few others have persisted in trying to warn the public about radiation's dangers, but government and the radiation industries have been able to limit their ability to publish, while investing hugely in a continuing campaign to discredit them and to convince the public that "a little radiation is harmless."

When any radiation interacts with a substance, the electrons are the most responsive parts of the material, and some electrons are susceptible to being significantly changed even by low energy radiation, such as red light. As the energy of the radiation increases, more electrons are susceptible to activation. Blue light interacts with more electrons than yellow light, and ultraviolet light activates even the electrons in fairly stable molecules. X-rays and gamma rays will radically disrupt electrons in all biological molecules.

Several decades ago, it was conventionally taught that visible light is "chemically inert," and that ultraviolet, x-rays and gamma rays are "chemically active." I don't think there was ever any good scientific reason for that dichotomous belief, except that it was obvious that the more energetic rays were chemically active to a dangerous degree. Blue light is now known to be toxic to the eye, by activating the oxidation of polyunsaturated fatty acids; it has been known to be toxic to various cells, including plant cells, for more than 50 years. In the eye, blue light creates free radicals in melanin, which catalyze the oxidations. Other molecules, including porphyrins and vitamins, produce free radicals when exposed to blue light, ultraviolet, and the higher energy rays. For example, riboflavin, vitamin B2, when exposed to white light, can cause the vitreous body of the eye to liquefy by causing the depolymerization of hyaluronic acid, and in the skin it probably contributes to the age-related and sun-related loss of hyaluronic acid in the connective tissue. Ultraviolet light can attack the same molecules as blue light, but in addition it can dislodge electrons from many more molecules, including the tryptophan, tyrosine, and cystine in proteins.

The pro-oxidant effect of riboflavin in ordinary light is increased by its reactions with tryptophan, folic acid, vitamin B6 (pyridoxine), and tyrosine (Grzelak, et al., 2001). Higher energy radiation causes a spreading excitation of even more substances.

Although each part of an organism has its own complex ways of responding to the disturbance of its electrons by radiation, I think it's useful to think of some simple physical examples of how substances are changed by radiation.

Some topaz crystals that are colored when they are mined, quickly fade when they are exposed to bright light. Over a very long time, natural radiation displaced some electrons from the atoms in the buried crystals, and trapped them in "color centers," where they can absorb certain frequencies of low energy visible light, creating colors, without immediately escaping their traps. Bright light can gradually free the electrons from their "traps," bleaching the color. Glass that was made around 1900 often turned purple when it was left in the sun, because ultraviolet light had enough energy to create trapped electrons in that material; heating the glass to a few hundred degrees was enough to bleach the color. Diamonds, salt, and many other materials can be colored artificially with high energy radiation, and they can be bleached by the lower energy of another type of radiation, or by heating, or by ultrasound.

When trapped electrons are released by heating, and return to their relaxed ground state, they give up energy as thermoluminescence. The amount of thermoluminescence can be used to measure the dose of radiation the material was exposed to.

The intensity of the color induced by radiation is another way of judging the material's radiation exposure.

Another way to measure the accumulated dose of radiation is to use an instrument that measures the resonance of unpaired electrons, color centers or free radicals, with a microwave field--these EPR or ESR (electron paramagnetic resonance or spin resonance) machines can measure unpaired electrons in living tissue, and can distinguish different environments of the electrons, analogous to the colors seen in transparent materials.

EPR and thermoluminescence can be used to determine the accumulated radiation exposure of teeth, bones, and rocks. Since natural radiation from minerals and cosmic rays is steady over long periods of time at a particular location on the earth, these techniques can be used for archeological and geological dating. After radiation accidents, tooth enamel can accurately determine the dose received, except that the person's dental history must be known, so that dental radiation can be subtracted from the accidental exposure.

In liquids, trapped electrons quickly return to the ground state, because of the greater mobility of atoms and ions in liquids, but while water is being exposed to intense gamma rays, the "solvated electrons" give the water an intense blue color. In ice, the trapped electrons have a long life-time.

In hair, skin, plant materials, and other tissues, the trapped electrons decay much more quickly than in teeth and bones, but their effects can be seen for 50 years or more, as for example the increased amount of amyloid seen in Japanese survivors of the atomic bomb.

Hours after a person has been in the sunlight, EPR can detect free radicals in the melanin pigment in hair. In the skin, the melanin radicals decay more quickly, but the ultraviolet-induced spreading free radicals can still be detected in the skin hours later, during the time in which the sunburn injury is reaching its peak. Applying antioxidants and red light to irradiated tissues soon after exposure can profoundly decrease the injury. The beneficial effects of sunlight are largely the result of the red part of the spectrum, which penetrates deeply into tissues, and helps to inactivate toxic electrons.

When a dose of radiation similar to a diagnostic x-ray is given to cells in culture, they are still emitting induced light after an hour or more (Vicker, et al., 1991). The genetic mutations produced by radiation are still occurring hours or days after the exposure; the observations in the Japanese suggest that they might keep occurring years after the exposure. In cell culture, they can appear in unirradiated cells after 30 cell-doublings, the equivalent of a person's lifetime. In a form of imprinting, the radiation injury can be passed to a later generation. The radiation creates genetic instability, rather than just immediate direct mutations. Stress and estrogen exposure cause genetic instability, probably because of the lingering metabolic effects, which

are similar to those caused by radiation. The metabolic changes causing delayed mutations seem to be those involved in inflammation (Wright, 2004).

The electrons which are physically excited by high energy radiation are absorbed by various molecules, causing chemical excitation and chemical reactions, which produce "chemiluminescence" similar to that seen after any injury. In some cases these abnormally reactive chemicals cause the familiar kinds of damage, such as broken chromosomes or chain reactions of lipid peroxidation in the polyunsaturated fats. Various stresses and metabolic conditions are known to be passed on to daughter cells and to germ cells and offspring as alterations in the degree of methylation of certain genes, but this process of "epigenetic inheritance" and imprinting has hardly been investigated, because of the fear of "Lamarckism" that dominated biomedical research in the U.S. in the twentieth century.

Between chemiluminescence and the actual biological processes of growth, differentiation, movement, inheritance, and disease there is an immense zone of ignorance, that has been excluded from organized scientific investigation, because corporate financial interests have preferred mechanical reductionist dogmas such as "neodarwinian molecular biology."

The experiments of Alexander Gurwitsch (or Gurvich) and his wife in the 1920s and 1930s that showed that growing cells stimulated waves of cell division in cells in a nearby compartment, separated by a thin quartz glass partition, and that the stimulation occurred only when the partition glass was able to transmit ultraviolet rays, had immense implications for medicine and biology. Fritz Popp and Mae-Wan Ho have validated and extended the discoveries of the Gurwitsches, using new devices that confirm the nature of the radiation.

Everyone working with radiation now recognizes that external ultraviolet rays, at different wavelengths and intensity, can stimulate or inhibit cell division, and can cause cells to die prematurely or to become immortalized tumor cells, but only a very few researchers, in the last six years, have begun to see the intimate connections between ultraviolet light and the cells' systems of interaction and self-regulation. The universities have inculcated the doctrine that "radiation damages by mutating genes." People talk about DNA being altered when it is "hit" by radiation, and everyone who has taken a biology course has probably heard that the "target size" of a gene or a virus determines the likelihood that it will be damaged by a given dose of radiation. That quaint relic of primitive radiation biophysics is useful for nuclear power corporations, and for dentists, and for anyone who wants to sell whole body scans to the public. But that dogma has now been very firmly knocked out by hundreds of direct hits by experimental data, that show that irradiated cells transmit something to other cells that weren't exposed to the radiation, in a "radiation bystander effect."

In the 1950s, Alice Stewart began a series of studies that showed that medical x-rays were causing a large number of cancers in children. At that time, physicians were taught that the "threshold" of safety for fetal x-ray exposure was ten rads. (In animal studies, that dose reduces brain size, and causes mental retardation.) In her first study, she and David Hewitt, a statistician who had noticed that leukemia deaths in children had recently increased by 50%, found that leukemia deaths were twice as high among children whose mothers had received pelvic x-rays during their pregancy, compared to other women. The supposedly safe dose of a half to one rad was producing those effects. Even a single x-ray was harmful. If the fetus was x-rayed during its first three months, the leukemia rate was increased 10-fold. Miscarriages, malformations and brain cancers were also more common in the x-rayed patients. Even having been x-rayed before pregnancy was found to harm the babies a woman would later have. Stewart's study was widely denounced, and she lost her funding and staff at Oxford.

Her results probably understated the actual harm of medical x-rays, since the control patients who didn't receive x-rays were still being exposed to the radioactive fallout from the testing of atomic bombs.

For many years, it has been clear that low birth weight (below 5.5 pounds) was associated

with subnormal mental abilities. Recently, studies of women who had dental x-rays while pregnant show that their risk of having a low birth weight infant was increased. Those whose radiation dose was in the 90th percentile of the group studied were 3.61 times as likely as the unexposed women to have a full-term low birth weight baby (Hujoel, et al., 2004).

Estrogen excess during pregnancy is known to retard fetal development. The effects of dental x-rays on the brain, pituitary and thyroid gland probably played a role in causing the pregnancy abnormalities, but any tissue which is exposed to x-rays will tend to begin producing estrogen. With aging, most tissues begin to form estrogen synthetase, the enzyme that converts androgens into estrogen, and radiation accelerates that process. Many years ago, researchers noticed that x-rays or gamma rays would cause a female animal to go into estrus, as if it had been treated with estrogen, and it was assumed that the radiation had stimulated the brain and pituitary to produce gonadotropic hormones that activated the ovaries. However, other researchers found that simply irradiating an animal's foot would induce estrus. Radiation activates many of the mediators of inflammation, including interleukin-6, which activates estrogen synthetase.

Estrogen does many things to retard intrauterine growth and development, and most of those effects are prevented by adequate progesterone, which keeps estrogen out of cells even when the blood level of estrogen is very high. Animals that gestate under the influence of excessive estrogen (if they survive) have a small brain, and the cortex, the highest part of the brain, is thinner than normal. Just by acting on the mother's metabolism, reducing her ability to deliver oxygen and glucose and other nutrients, radiation and the estrogen it induces will damage the fetal brain.

In the brain, interleukin-6 is associated with cognitive decline, progressive dementia, so if the dental x-rays are acting primarily through the brain, the mothers who bore under-developed infants will probably suffer an increased incidence of Alzheimer's disease.

Ernest Sternglass and Jay Gould showed clearly that declining SAT scores (especially the absolute number of students reaching the highest scores) followed the intensity of radiation from nuclear fallout in each region of the country, with a lag of 18 years, indicating that the students taking the tests were affected during their gestation.

The Nuclear Energy Institute, and other agents and apologists for the nuclear industry, are still engaged in an intense campaign to discredit Sternglass, by quoting denunciations by "important" newspaper editorial writers and government officials. (And by hiring ghost writers to provide articles for professors to submit to their local newspapers as their own work.) Irrational and dishonest "arguments" of that sort, unfortunately, are effective in controlling the public's behavior. It probably doesn't help that the generations most affected by the brain damaging radiations are now at the age--41 to 56--that has the most social, political, and economic power.

Studies of prenatal radiation exposure in Japan show clearly that it reduces brain size, intelligence, and school achievement (Fujiwara, et al., 1994; Miller, 1988; Mole, 1990; Otake and Shull, 1993; Shigematsu, 1994; Yamazaki and Shull, 1990)

Academic scientists know where their money comes from, and so the enemies of corporate/governmental/military science are adopted as enemies by academic science, and students aren't given the opportunity to examine the alternative ideas.

The functions of proteins are governed by their complex shapes. Enzyme activity depends on particular conformations of the protein, to create catalytic fields in the right places. The conformation of the protein depends on both external conditions (solvent and solutes, pH, temperature, oxidation-reduction potential of the system, for example) and internal fields within the protein itself. Simply changing the state of an electron can change the function of an enzyme, leading to widespread changes in cellular physiology.

The cell, especially the cytoplasm, functions as a system, and disturbance of its electrons will affect it systematically, modifying regulatory processes at all levels, and coordinating the

activities of enzymes. A certain intensity of stress will activate the processes of inflammation.

Three important kinds of enzymes that are activated by stress and radiation are phospholipases (that release fatty acids), tryptophan hydroxylase (that controls the conversion of tryptophan to serotonin), and aromatase (estrogen synthetase, that converts androgens to estrogen). The products of these enzymes stimulate cell division, and produce features of the inflammatory process, including the leakiness of capillaries.

Since these processes are similar, regardless of the source of the disturbance, the basic antistress and antiinflammatory systems that protect against common imbalances (such as fluctuations in glucose and oxygen) will also be somewhat protective against radiation injury.

The thyroid hormone is probably the basic protective hormone against radiation, as it is against other stressors. Besides helping to provide the energy needed to repair genetic damage and to protect against calcium overload, the thyroid hormones help to dissipate excited electrons, and reduce lipid peroxidation and the chemiluminesce produced by radiation. A dose of thyroid 50% larger than the normal physiological daily production can reduce radiation damage by 30% to 40% (Antipenko and Antipenko, 1994).

Progesterone has antioxidant functions, as well as suppressing the mediators of inflammation, and inhibiting the enzymes that produce free fatty acids (and the associated prostaglandins), serotonin and estrogen. Cortisol is protective against the acute inflammatory effects of radiation (Beetz, et al., 1997), but progesterone has those effects without the harmful effects of excess cortisol.

Aspirin and vitamin E are protective against toxic radiation, and the consequent inflammatory processes.

Saturated fats have many of the same functions, inhibiting inflammation, capillary leakiness, and the free radical chain reactions.

Niacinamide, by reducing lipolysis, would be another antiinflammatory agent that could help to interrupt the degenerative processes initiated by exposure to radiation.

Radiation stops repair processes in the brain, but there is evidence that treatment with an antiinflammatory drug (indomethacin) can restore the reparative process of nerve cell formation (Monje, et al., 2003).

The normal sequence in aging, proceeding from inflammation to atrophy and then to disordered repair or cancer, is accelerated by radiation exposure. Harry Rubin demonstrated that cancer precedes genetic change, rather than being "caused by genetic mutations," as the dogmatists have claimed. The existence of a "cancer field" has been known for a long time, but the doctrine of the "mutant cancer cell" has held that a single mutation, or a series of mutations, in a single cell is the cause of all cancers, and has denied that the cell's interactions with its neighbors are responsible for its properties. Recent radiation research is showing that "inflammatory imprinting" precedes both cancer and mutations.

In recent years, inflammation's role in cancer and heart disease has been acknowledged to some extent, and simple antiinflammatory treatments such as aspirin have been more widely accepted in the prevention and treatment of both heart disease and cancer. I think the next step is to recognize the importance of preventing all sorts of inflammation during the reproductive years, to protect the brains of the unborn, and the inheritance of future generations.

If the Gurviches, and Fritz Popp and Mae-Wan Ho are right, the investigation of light's role in life has hardly begun, and the possible therapeutic uses of light haven't been imagined yet. Their idea of "the coherent organism" is giving an expanded meaning to the idea of a biological "field."

But for the present, we should know enough to avoid all exposure to x-rays and radioactive isotopes, and to make sure that we get enough sunlight, without too much sunburn.

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Ray Peat's Newsletter

"Senescence has no function—it is the subversion of function." Alex Comfort

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Osteoporosis, aging, tissue renewal, and product science

The incidence of osteoporosis, like obesity, has been increasing in recent decades. The number of hip fractures in many countries has doubled in the last 30 or 40 years (Bergstrom, et al., 2009). An exception to that trend was Australia in the period between 2001 and 2006, where the annual incidence of hip fractures in women over 60 years old decreased by 28.3%. During those years, the number of prescriptions for "hormone replacement therapy" decreased by 54.6%, and the number of prescriptions for bisphosphonate increased by 245%. The publication of the Women's Health Initiative results in 2002 (showing that the Prem-Pro treatment caused breast cancer, heart attacks, and dementia), led to a great decrease in the use of estrogen treatments everywhere.

After the FDA approved estrogen's use in 1972 for the prevention of osteoporosis the number of women using it increased greatly, and by 1994, 44% of women in the US had used it. After the WHI results were published, the number of prescriptions for "HRT" fell by more than half, and following that decrease in estrogen sales, the incidence of breast cancer decreased by 9% in women between the ages of 50 and 54.

With the incidence of hip fractures increasing while the percentage of women using estrogen was increasing, it seems likely that there is something wrong with the theory that osteoporosis is caused by an estrogen deficiency. That theory was derived from the theory that menopause was the consequence of ovarian failure, resulting from the failure to ovulate and produce estrogen when the supply of eggs was depleted. The theory was never more than an ideological preference, but the estrogen industry saw it as an opportunity to create a huge market.

There are many studies that seem to imply that the greater incidence of osteoporotic fractures among women is the result of their exposure to estrogen during their reproductive years. This would be analogous to the understanding that it is the cumulative exposure to estrogen that ages the nerves in the hypothalamus that control the cyclic release of the gonadotropic hormones, causing the menopause.

. . . the nature of science itself changed around the middle of the last century, becoming product and disease oriented, so that now relatively few people are continuing to study bones objectively.

Animal studies show that estrogen stunts growth, including bone growth. The high estrogen levels in girls' teen years and early twenties accounts for the fact that women's bones are lighter than men's. In rat studies, treatment with estrogen was found to enlarge the space between the jawbone and the teeth, which is a factor in periodontal disease (Elzay, 1964). Teeth are very similar to bones, so it's interesting that treating male or female rats with estrogen increases their incidence of tooth decay, and removing their gonads was found to decrease the incidence (Muhler and Shafer, 1952). Supplementing them with thyroid hormone decreased the incidence of cavities in both males and females (Bixler, et al., 1957).

One of the "estrogen receptors" appears to actively contribute to bone loss (Windahl, et al., 1999, 2001). Studies in dogs following the removal of their ovaries found that there was an increase of bone remodeling and bone formation

rate in the first month, followed by a few months of slowed bone formation, but that by 10 months after the surgery the bones had returned to their normal remodeling rate, and that "at no time was a significant reduction in bone volume detected" (Boyce, et al., 1990). With the removal of the ovaries, the production of progesterone as well as estrogen is affected, but the adrenal glands and other tissues can produce those hormones.

Until the influence of the estrogen industry overwhelmed it, ordinary science was studying bone development in comprehensive ways, understanding its biological roles and the influences of the environment on it. But the nature of science itself changed around the middle of the last century, becoming product and disease oriented, so that now relatively few people are continuing to study bones objectively.

The outstanding physical-chemical property of bone is that it is a reservoir-buffer of carbon dioxide, able to bind huge amounts of the gas into its structure.

When carbon dioxide increases in the bloodstream it is at first absorbed rapidly by the bones, and if the blood level of CO2 is kept high day after day, the rate of absorption gradually slows down, but in experiments that have continued for several weeks the bones were still slowly absorbing more carbon dioxide; the absorption curve seems to be asymptotic. When people move to or from high altitudes, their bones appear to continue adapting to the different gas pressures for years. A reduction of atmospheric pressure (which allows the tissues to retain more carbon dioxide) helps to reduce the calcium loss caused by immobility (Litovka and Berezovs'ka, 2003; Berezovs'kyi, et al., 2000), and promotes the healing of damaged bone (Bouletreau, et al., 2002). Ultrasound treatment, which accelerates bone healing, stimulates processes similar to reduced oxygen supply (Tang, et al., 2007).

The mineral in newly formed bone is calcium carbonate, and this is gradually changed to include a large amount of calcium phosphate. Besides forming part of the mineral, carbon dioxide is also incorporated into a protein (in a process requiring vitamin K), in a process that causes this protein, osteocalcin, to bind calcium. The osteocalcin protein is firmly bonded to a collagen molecule. Collagen forms about 30% of the mass of bone; several percent of the bone consists of other organic molecules, including osteocalcin, and the rest of the mass of the bone consists of mineral.

Thyroid hormone is essential for forming carbon dioxide. In the early 1940s, experimental rabbits were fed their standard diet, with the addition of 1% desiccated thyroid gland, which would be equivalent to about 150 grains of Armour thyroid for a person. They became extremely hypermetabolic, and couldn't eat enough to meet their nutritional needs for growth and tissue maintenance. When they died, all of their tissues weighed much less than those of animals that hadn't received the toxic dose of thyroid, except for their bones, which were larger than normal. Experiments with the thin skull bones of mice have shown that the active thyroid hormone, T3, increases the formation of bone. To increase cellular respiration and carbon dioxide production, T3 increases the activity of the enzyme cytochrome oxidase, which uses copper as a co-factor. Increased thyroid activity increases the absorption of copper from foods.

There is an inherited condition in humans, called osteopetrosis or marble bone disease, caused by lack of a carbonic anhydrase enzyme, which causes them to retain a very high level of carbon dioxide in their tissues. Using a chemical that inhibits carbonic anhydrase, such as the diuretic acetazolamide, a similar condition can be produced in animals. Acetazolamide inhibits the bone resorbing actions of parathyroid hormone, including lactic acid formation and the release of the lysosomal enzyme, beta-glucuronidase (Hall and Kenny, 1987).

While lactic acidosis causes bone loss, acidosis caused by increased carbonic acid doesn't; low bicarbonate in the body fluids seems to remove carbonate from the bone (Bushinsky, et al., 1993), and also mineral phosphates (Bushinsky, et al., 2003). The parathyroid hormone, which removes calcium from bone, causes lactic acid to be formed by bone cells (Nijweide, et al., 1981; Lafeber, et al., 1986). Lactic acid produced by intense exercise causes calcium loss from bone (Ashizawa, et al., 1997), and sodium bicarbonate increases

calcium retention by bone. Vitamin K2 (Yamaguchi, et al., 2003) blocks the removal of calcium from bone caused by parathyroid hormone and prostaglandin E2, by completely blocking their stimulation of lactic acid production by bone tissues. Aspirin, which, like vitamin K, supports cell respiration and inhibits lactic acid formation, also favors bone calcification. Vitamin K2 stimulates the formation of two important bone proteins, osteocalcin and osteonectin (Bunyaratavej, et al., 2009), and reduces the activity of estrogen by oxidizing estradiol (Otsuka, et al, 2005).

The formation of eggshell, which is mostly calcium carbonate, is analogous to the early stage of bone formation. In hot weather, when chickens pant and lower their carbon dioxide, they form thin shells. A sodium bicarbonate supplement improves the quality of the eggshell (Balnave and Muheereza, 1997; Makled and Charles, 1987). Chickens that habitually lay eggs with thinner shells have lower blood bicarbonate than those that lay thick shelled eggs (Wideman and Buss, 1985).

One of the arguments for stopping the sale of DDT in the US was that it was threatening to cause extinction of various species of bird because it caused them to lay eggs with very weak shells. Several other synthetic estrogenic substances, ethynylestradiol, lindane, PCBs, cause eggshell thinning, partly by altering carbonic anhydrase activity (Holm, et al, 2006). Estrogen and serotonin activate carbonic anhydrase in some tissues, progesterone tends to inhibit it. DDE, a metabolite of DDT, reduces medullary bone formation in birds (Oestricher, et al., 1971) and bone mineral density in men (Glynn, et al., 2000). Among its estrogenic effects, DDE increases prolactin (Watson, et al., 2007); one form of DDT inhibits progesterone synthesis and increases estrogen (Wojtowics, et al., 2007)

In youth, the mineralization of the collagen framework is slightly lower than in maturity, and the bones are more flexible. With aging, the mineralization increases progressively, and the proportion of collagen decreases slightly, and the bones become increasingly brittle. (Rogers, et al., 1952; Mbuyi-Muamba, et al., 1987).

Collagen is a major part of the extracellular substance everywhere in the body, and its concentration increases with aging in the non-calcified tissues. There is considerable renewal and modification of collagen, as new molecules are formed and old molecules broken down, but its average structure changes with aging, becomes less soluble and more rigid, as the result of chemical cross-links formed between molecules. These cross-links are involved in regulating the differentiation of bone cells (Turecek, et al., 2008). Recently (August 2, 2011), Deasey et al., have published evidence showing that cross-linking is required for bone mineralization (2011).

The outstanding physical-chemical property of bone is that it is a reservoir-buffer of carbon dioxide, able to bind huge amounts of the gas into its structure.

Around 1950, Fritz Verzar began studying the changes of collagen that occur with aging, and his work led to the "collagen theory of aging." He showed that older, stiffer, less elastic tendons have a higher "melting" or contracting temperature than young tendons. (This effect is responsible for the curling of a piece of meat when it is frying.)

Verzar and his colleagues investigated the effects of hormonal treatments on the aging of rat collagen, especially in their tail tendons. They found that estrogen treatment increased the stiffness and the melting temperature of collagenous tissues. While estrogen increased the cross-linking with aging, removing the pituitary gland was found to retard the aging.

Later, the cross-linking enzymes transglutaminase and lysyl oxidase, which are induced by estrogen, were found to be a major factor in the cross-linking of collagen and other molecules.

When estrogen was found to age the connective tissues, it was assumed that continual breeding during an animal's life-time, greatly increasing the total exposure of the tissues to estrogen, would increase the aged rigidity of the connective tissues, but these animals were found to have less rigid tissues. During pregnancy other hormones, especially progesterone, were also increased, and it was suggested that this reversed the effects of

aging and estrogen. Since most people had believed that frequent pregnancies would cause a woman to age more rapidly, a large survey of records was done, to compare the longevity of women with the number of pregnancies. It was found, in the very extensive Hungarian records, that life-span was increased in proportion to the number of pregnancies.

Despite these very interesting results in the 1950s and 1960s, the growing influence of the estrogen industry changed the direction of aging research, favoring the belief that decreasing estrogen accelerated the deterioration of tissues in aging, and the popularity of Denham Harman's "free radical theory of aging" led many people to assume that random reactions produced by lipid peroxidation were responsible for most of the cross-linking, and that theory was gradually replaced by the "glycation" theory of aging, in which sugar molecules break down and form the cross-links, by random, non-enzymic processes. Estrogen's role in aging was completely by-passed.

The meat industry is interested in reducing the toughness of meat, by influencing the nature of the collagen in muscle. Castrated animals were found to produce meat that was tenderer than that of intact males. When castrated animals were treated with testosterone, the amount of collagen was increased, making the meat tougher. But when dihydrotestosterone, which can't be converted to estrogen was used, the meat didn't become tough. Treatment with estrogen produced the same increase of collagen as treatment with testosterone, showing that testosterone's effect was mainly the result of its conversion to estrogen (Miller, et al., 1990).

In the 1960s and '70s the estrogen industry was looking for ways to build on the knowledge that in puberty estrogen is responsible for accelerating the calcification of the growth plate at the ends of the long bones, and to find a rationale for selling estrogen to all women concerned with the problems of aging. As bone metabolism was investigated, two kinds of cell were found to be active in constantly remodeling the bone structure: Osteoclasts (breaking it down), and osteoblasts (building new bone). Estrogen was found to slow the actions of the osteoclasts, so the idea that it would delay osteoporosis became the basis for a huge new marketing campaign. Slowing bone metabolism became the focus. Although estrogen was known to increase prolactin, and prolactin was known to accelerate bone loss, nearly all publications began to focus on substances in the blood or urine that corresponded to the rate of bone turnover, with the implication that increasing bone turnover would correspond to a net loss of bone.

This was the context in which, during the 1980s, articles about thyroxine's role in causing osteoporosis began to appear. The thyroid hormone supports bone renewal, and increases indicators of bone breakdown in the blood and urine. If estrogen's use was to be justified by slowing bone turnover, then the effects of thyroid, accelerating bone turnover, should be interpreted as evidence of bone destruction.

A basic problem with many of the publications on thyroid and bone loss was that they were talking about an unphysiological medical practice (prescribing the pre-hormone, thyroxine), which frequently failed to improve thyroid function, and could even make it worse, by lowering the amount of T3 in the tissues.

Later, it was noticed that high TSH was associated with the signs of lower bone turnover. TSH rises when there is less thyroid hormone, but (after the recombinant TSH became available for medical use) a few publications argued that it was the TSH itself, rather than the absence of thyroid hormone, that was "protecting" the bones (lowering the evidence of bone turnover). The doctrine that had been developed to support estrogen therapy was now used to oppose thyroid therapy. Keeping the TSH high would slow bone turnover.

Working in this cultural context, genetic engineers at Amgen identified a protein that inhibited the formation of osteoclast cells, and slowed bone metabolism. It was suggested that it was responsible for estrogen's suppression of the osteoclasts, and many publications appeared showing that it was increased by estrogen. It was named "osteoprotegerin," meaning "the bone protecting protein." Prolactin increases osteoprotegerin (OPG), reducing bone resorption just as estrogen does. Serotonin also increases OPG, and

it turns out that OPG is elevated in all of the pathological conditions associated with high serotonin, including cancer, pulmonary artery hypertension, vascular calcification, and even bone loss.

While Arthur Everitt, Verzar, and others were studying the effects of the rat's pituitary (and other glands) on collagen, W. D. Denckla investigated the effects of reproductive hormones and pituitary removal in a wide variety of animals, including fish and mollusks. He had noticed that reproduction in various species (e.g., salmon) was quickly followed by rapid aging and death. Removing the pituitary gland (or its equivalent) and providing thyroid hormone, he found that animals lacking the pituitary lived much longer than intact animals, and maintained a high metabolic rate. Making extracts of pituitary glands, he found a fraction (closely related to prolactin and growth hormone) that suppressed tissue oxygen consumption, and accelerated the degenerative changes of aging.

Aging, estrogen, cortisol, and a variety of stresses, including radiation and lipid peroxidation, chemically alter collagen, producing cross-links that increase its rigidity, and affect the way it binds minerals. The cross-linking enzymes induced by estrogen are involved in the normal maturation of bone collagen, and at puberty when estrogen increases, bone growth is slowed, as the cross-linking and mineralization are accelerated. With aging and the accumulation of heavy metals and polyunsaturated fats, random oxidative processes increase the cross-linking. In bones, the relatively large masses of cartilage absorb oxygen and nutrients slowly, so internally the amount of oxygen is very limited, about 1/5 as much as at the surface, and this low oxygen tension is an important factor in regulating growth, differentiation, cross-linking, and calcification, maintaining bone integrity. But in blood vessels the connective tissues are abundantly supplied with oxygen and nutrients; this is normally a factor regulating the production of collagen and its cross-linking, and preventing calcification.

When the factors promoting collagen synthesis and maturation are increased systemically, with aging and stress, the excess cross-linking slows the biological renewal process in bones, but in blood vessels the same processes creating excess cross-linking initiate a calcification process, involving the various factors that in youth are responsible for normal maturation of bone.

Prolactin, like estrogen, interferes with thyroid function and oxygen consumption (Wade, et al., 1986; Strizhkov, 1991; Spatling, et al., 1982). Many years ago, repeated lactation was considered to cause osteoporosis and loss of teeth, and prolactin, which mobilizes calcium from bones for the production of milk, was recognized as an important factor in bone loss. Drugs that increase prolactin were found to cause osteoporosis. In the 40 years since the drug industry began its intense promotion of estrogen to prevent and treat osteoporosis, there has been very little attention to the fact that estrogen increases prolactin, which contributes to osteoporosis, but some people (e.g., Horner, 2009) have noticed that oral contraceptives and menopausal hormone treatments have damaged the bones of the inner ear, causing otosclerosis and impaired hearing, and have suggested that prolactin mediates the effect.

A few years ago, the "serotonin reuptake inhibitor" antidepressants, already known to increase prolactin by increasing the effects of serotonin, were found to be causing osteoporosis after prolonged use. Estrogen increases serotonin, which besides promoting the secretion of prolactin, also stimulates the production of parathyroid hormone and cortisol, both of which remove calcium from bone, and contribute to the calcification of blood vessels. The association between weakened bones and hardened arteries is now widely recognized, but researchers are being careful to avoid investigating any mechanisms that could affect sales of important drug products, especially estrogen and antidepressants.

Following the recognition that the SSRI drugs were causing osteoporosis, it was discovered that the serotonin produced in the intestine causes bone loss, and that inhibiting intestinal serotonin synthesis would stop bone loss and produce a bone building anabolic effect (Inose, et al., 2011). One group that had been concentrating on the interactions of genes commented that, recognizing the effects of intestinal serotonin, they had

suddenly become aware of "whole organism physiology" (Karsenty and Gershon, 2011).

In previous newsletters I have talked about the ability of intestinal irritation and the associated increase of serotonin to cause headaches, asthma, coughing, heart and blood vessel disease, muscular dystrophy, flu-like symptoms, arthritis, inflammation of muscles and nerves, depression, and inflammatory brain diseases. With the new recognition that serotonin is a basic cause of osteoporosis, intestinal health becomes a major issue in aging research.

The protein that inhibits intestinal formation of serotonin is the low density lipoprotein receptor-related protein. This seems likely to have something to do with the fact that "low" HDL is associated with better bones. A low level of LDL is associated with increased vertebral fractures (Kaji, et al., 2010).

Cartilage synthesis and turnover are highest at night. It is inhibited by metabolic acidosis (increased lactic acid), but not by respiratory acidosis (CO_2) (Bushinsky, 1995). Since most calcium is lost from bone during the night (Eastell, et al., 1992; even in children: DeSanto, et al., 1988) in association with the nocturnal rise of the catabolic substances, such as free fatty acids, cortisol, prolactin, PTH, and adrenalin, things which minimize the nocturnal stress can decrease the bone turnover. These include calcium (Blumsohn, et al., 1994) and sugar. Catabolic substances and processes increase with aging, especially at night. Babies grow most during the night when bone turnover is high, and even a daytime nap accelerates collagen turnover (Lutchman, et al., 1998).

Discussions about whether a certain person's osteoporosis is "menopausal osteoporosis" or "senile osteoporosis" have neglected the possibility that osteoporosis doesn't begin in either menopause or old age, but that it is the result of life-long developmental processes that interact with all the factors that are involved in aging. The fact that the collagen content of old bone is lower than in young bone (as a percentage of bone weight) shows that the problem in osteoporosis isn't a lack of calcification, it's a deficiency of tissue renewal, parallel to sarcopenia, the decrease of muscle mass with aging. Systemically decreased tissue renewal would account for the association of bone loss with other processes such as male baldness (Morton, et al., 2007) and Alzheimer's disease (Zhou, et al., 2011, Duthie, et al., 2011).

A high level of respiratory energy production that characterizes young life is needed for tissue renewal. The accumulation of factors that impair mitochondrial respiration leads to increasing production of stress factors, that are needed for survival when the organism isn't able to simply produce energetic new tissue as needed. Continually resorting to these substances progressively reshapes the organism, but the investment in short-term survival, without eliminating the problematic factors, tends to exacerbate the basic energy problem. This seems to be the reason that Denckla's animals, deprived of their pituitary glands, but provided with thyroid hormone, lived so long: they weren't able to mobilize the multiple defenses that reduce the mitochondria's respiratory energy production.

Several things that the geneticists would never be able to fit into their schemes of "bone regulatory molecules" such as OPG, growth hormone, parathyroid hormone, and estrogen, fit neatly with the idea that bone health is maintained by respiratory energy and tissue renewal, under the influence of thyroid hormone. For example, adrenaline, which is increased by stress, aging, and hypothyroidism (and in many cases by estrogen), causes bone loss. Even the bone loss caused by immobility can be blocked by an adrenaline blocker such as propranolol. (The stress of immobility also famously increases serotonin.) Adrenaline tends to decrease carbon dioxide and increase lactic acid, and it strongly increases parathyroid hormone (Ljunhgall S, et al., 1984).

Calcium activates mitochondrial respiration, and lowers adrenaline (Luft, et al., 1988), parathyroid hormone (Ohgitani, et al., 1997), and prolactin (Kruse and Kracht, 1981). Copper, which is the co-factor for the cytochrome C oxidase enzyme, activated by thyroid, is essential for bone formation and maintenance, and is consistently deficient in osteoporosis. Thyroid hormone increases the body's ability to assimilate copper.

Aspirin, which stimulates bone formation, has other thyroid-like actions, including activation of

mitochondrial respiration and energy production, with an increase of cytochrome C oxidase (Cai, et al., 1996), and it lowers serotonin (Shen, et al., 2011). It also apparently protects against calcification of the soft tissues, (Vasudev, et al., 2000), though there has been surprisingly little investigation of that. "Aspirin can promote trabecular bone remodeling, improve three-dimensional structure of trabecular bone and increase bone density of cancellous in osteoporotic rats by stimulating bone formation. It may become a new drug for the treatment of osteoporosis" (Chen, et al., 2011).

A wide range of inflammatory mediators that accelerate inflammation and bone loss also inhibit thyroid function. People who ate more polyunsaturated fat, which inhibits thyroid and oxidative metabolism, were several times more likely to have osteoporotic fractures (that is, essentially spontaneous fractures) than people who ate the least (Martinez-Ramirez, et al., 2007).

Arachidonic acid stimulates prolactin secretion, and prolactin acts on the thyroid gland to decrease its activity, and on other tissues to increase their glycolysis (with lactate production), while decreasing oxidative metabolism (Spatling, et al., 1982; Strizhkov, 1991).

Living at high altitude, which strengthens bones, increases thyroid activity and decreases prolactin (Richalet, et al., 2010) and parathyroid hormone (Khan, et al., 1996). It lowers free fatty acids, which lower bone mass by reducing bone formation and increasing bone resorption (Chen, et al., 2010). In menopausal women, polyunsaturated fatty acids and even monounsaturated fats are associated with bone loss, fruit and vegetable consumption protects against bone loss (Macdonald, et al., 2004).

While it's very interesting that the drug propranol which blocks adrenaline, and drugs that block serotonin formation, have bone protective and restorative effects, they also have undesirable side effects. Food choices that optimize oxidative metabolism are the safest, as well as the most economical, way to approach the problem of osteoporosis and other degenerative changes. A person can easily perceive changes in appetite, quality of sleep, changes in skin, hair, and mood, etc., but blood tests could be used to confirm that the right choices were being made. Tests for vitamin D, parathyroid hormone, free fatty acids, and CO2/bicarbonate, as well as the hormones, can be helpful, if a person isn't sure whether their diet, sunlight exposure, and thyroid supplementation is adequate.

The popular medical understanding of the organism is based on a mechanistic view of causality, in which genes have a central role, causing things to develop and function in certain ways, and that hormones and drugs can cause genes to increase or decrease their activity. Genes that build bones can be activated by one substance, and genes that tear down bones can be inhibited by another substance. The "osteoprotegerin" story illustrates the problem with that kind of thinking.

Vernadsky's description of an organism as a "whirlwind of atoms" is probably a better way to think of how "causality" works. The moving air in a whirlwind forms a self-intensifying system, with the motion reducing the pressure, causing more air to be drawn into the system. The atoms moving in coordination aren't acting as separate things, but as parts in a larger thing. The way in which increased metabolism in the bones acts favorably on the metabolism of kidneys, blood vessels, lungs, liver, digestive system, etc., which in turn favors the bones' renewal, is analogous to the tendency of a whirlwind to intensify as long as there is a source of energy. **The intensity of oxidative metabolism is the basic factor that permits continuing coordination of activity, and the harmonious renewal of all the components of the organism.**

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Ray Peat's Newsletter

"Nothing in the world is more dangerous than sincere ignorance and conscientious stupidity." **Martin Luther King Jr.**

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Sugar Issues

Since the first doctor noticed, hundreds of years ago, that the urine of a diabetic patient tasted sweet, it has been common to call the condition the sugar disease, or sugar diabetes, and since nothing was known about physiological chemistry, it was commonly believed that eating too much sugar had to be the cause, since the ability of the body to convert the protein in tissues into sugar wasn't discovered until 1848, by Claude Bernard (who realized that diabetics lost more sugar than they took in). Even though patients continued to pass sugar in their urine until they died, despite the elimination of sugar from their diet, medical policy required that they be restrained to keep them from eating sugar. That prescientific medical belief, that eating sugar causes diabetes, is still held by a very large number, probably the majority, of physicians.

Originally, diabetes was understood to be a wasting disease, but as it became common for doctors to measure glucose, obese people were often found to have hyperglycemia, so the name diabetes has been extended to them, as type 2 diabetes. High blood sugar is often seen along with high blood pressure and obesity in Cushings syndrome, with excess cortisol, and these features are also used to define the newer metabolic syndrome.

Following the old reasoning about the sugar disease, the newer kind of obese diabetes is commonly blamed on eating too much sugar. Obesity, especially a fat waist, and all its associated health problems, are said by some doctors to be the result of eating too much sugar, especially fructose. (Starch is the only common carbohydrate that contains no fructose.) Obesity is associated not only with diabetes or insulin resistance, but also with atheroslcerosis and heart disease, high blood pressure, generalized inflammation, arthritis, depression, risk of dementia, and cancer.

There is general agreement about the problems commonly associated with obesity, but not about the causes or the way to prevent or cure obesity and the associated conditions.

In an earlier newsletter, I wrote about P. A. Piorry in Paris, in 1864, and Dr. William Budd in England, in 1867, who treated diabetes by adding a large amount of ordinary sugar, sucrose, to the patient's diet. Glucose was known to be the sugar appearing in the diabetic's urine, but sucrose consists of half glucose, and half fructose. In 1874, E. Kulz in Germany reported that diabetics could assimilate fructose better than glucose. In the next decades there were several more reports on the benefits of feeding fructose, including the reduction of glucose in the urine. With the discovery of insulin in 1922, fructose therapy was practically forgotten, until the 1950s when new manufacturing techniques began to make it economical to use.

Its use in diabetic diets became so popular that it became available in health food stores, and was also used in hospitals for intravenous feeding. However, while fructose was becoming popular, the cholesterol theory of heart disease was being promoted. This was the theory that eating foods containing saturated fat and cholesterol caused heart disease. (My newsletter, Cholesterol, longevity, intelligence, and health, discussed the development of that theory.)

A Swedish physician and researcher, Uffe Ravnskov, has reviewed the medical arguments for the theory that lipids in the blood are the cause of atherosclerosis and heart disease, and shows that there has never been evidence of causality, something which some people, such as Broda Barnes, understood from the beginning. In the 1950s, an English professor, John Yudkin, didn't

accept the idea that eating saturated fat was the cause of high blood levels of triglycerides and cholesterol, but he didn't question the theory that lipids in the blood caused the circulatory disease. He argued that it was sugar, especially the fructose component of sucrose, rather than dietary fat, that caused the high blood lipids seen in the affluent countries, and consequently the diseases. He was sure it was a specific chemical effect of the fructose, because he argued that the nutrients that were removed in refining white flour and white sugar were insignificant, in the whole diet.

Following the publication of Yudkin's books, and coinciding with increasing promotion of the health benefits of unsaturated vegetable oils, many people were converted to Yudkin's version of the lipid theory of heart disease, i.e., that the "bad lipids" in the blood are the result of eating sugar. This has grown into essentially a cult, in which sugar is believed to act like an intoxicant, forcing people to eat until they become obese, and develop the "metabolic syndrome," and "diabetes," and the many problems that derive from that.

The publicity campaign against "saturated fat" as an ally of cholesterol derived its support from the commercial promotion of the polyunsaturated seed oils as food for humans. Although the early investigators of vitamin E knew that the polyunsaturated oils could cause sterility, and others later found that their use in commercial animal foods could cause brain degeneration, there were a few biologists (mostly associated with George Burr) who believed that this type of fatty acid is an essential nutrient.

George and Mildred Burr had created what they claimed to be a disease in rats caused by the absence of linoleic or linolenic acid in their food. Although well known researchers had previously published evidence that animals on a fat free diet were healthy--even healthier than on a normal diet--Burr and his wife published their contradictory claim without bothering to discuss the conflicting evidence. I haven't seen any instance in which Burr or his followers ever mentioned the conflicting evidence. Although other biologists didn't accept Burr's claims, and several researchers subsequently published contrary results, he later became famous when the seed oil industry wanted scientific-seeming reasons for selling their product as an "essential" food. The fact that eating the polyunsaturated fats could cause the blood cholesterol level to decrease slightly was advertised as a health benefit. Later, when human trials showed that more people on the "heart healthy" diet died of heart disease and cancer, more conventional means of advertising were used instead of human tests.

Burr's experimental diet consisted of purified casein (milk protein) and purified sucrose, supplemented with a vitamin concentrate and some minerals. Several of the B vitamins weren't known at the time, and the mineral mixture lacked zinc, copper, manganese, molybdenum, and selenium. More of the essential nutrients were unknown in his time than in Yudkin's, so his failure to consider the possibility of other nutritional deficiencies affecting health is more understandable.

In 1933, Burr observed that his fat-deficient rats consumed oxygen at an extremely high rate, and even then, the thought didn't occur to him that other nutritional deficiencies might have been involved in the condition he described. Ordinarily, the need for vitamins and minerals corresponds to the rate at which calories are being burned, the metabolic rate. Burr recalled that the rats on the fat free diet drank more water, and he reasoned that the absence of linoleic or linolenic acid in their skin was allowing water vapor to escape at a high rate. He didn't explain why the saturated fats the rats were synthesizing from sugar didn't serve at least as well as a "vapor barrier"; they are more effective at water-proofing than unsaturated fats, because of their greater hydrophobicity. The condensed and cross-linked keratin protein in skin cells is the main reason for the skin's relatively low permeability. When an animal is burning calories at a higher rate, its sweat glands are more actively maintaining a normal body temperature, cooling by evaporation; the amount of water evaporated is an approximate measure of metabolic rate, and of thyroid function.

In 1936, a man in Burr's lab, William Brown, agreed to eat a similar diet for six months, to see whether the "essential fatty acid deficiency" affected humans as it did rats.

The diet was very similar to the rats', with a large part of the daily 2500 calories being provided at hourly intervals during the day by

sugar syrup (flavored with citric acid and anise oil), protein from 4 quarts of special fat-free skimmed milk, a quart of which was made into cottage cheese, the juice of half an orange, and a "biscuit" made with potato starch, baking powder, mineral oil, and salt, with iron, viosterol (vitamin D), and carotene supplemented.

Brown had suffered from weekly migraine headaches since childhood, and his blood pressure was a little high when he began the diet. After six weeks on the diet, his migraines stopped, and never returned. His plasma inorganic phosphorus declined slightly during the experiment (3.43 mg./100 cc. of plasma and 2.64 on the diet, and after six months on a normal diet 4.2 mg.%), and his total serum proteins increased from 6.98 gm.% to 8.06 gm.% on the experimental diet. His leucocyte count was lower on the high sugar diet, but he didn't experience colds or other sickness. On a normal diet, his systolic blood pressure varied from 140 to 150 mm. of mercury, the diastolic, 95 to 100. After a few months on the sugar and milk diet, his blood pressure had lowered to about 130 over 85 to 88. Several months after he returned to a normal diet, his blood pressure rose to the previous level.

On a normal diet, his weight was 152 pounds, and his metabolic rate was from 9% to 12% below normal, but after six months on the diet it had increased to 2% below normal. After three months on the sugar and milk diet, his weight leveled off at 138 pounds. After being on the diet, when he ate 2000 calories of sugar and milk within two hours, his respiratory quotient would exceed 1.0, but on his normal diet his maximum respiratory quotient following those foods was less than 1.0.

The effect of diabetes is to keep the respiratory quotient low, since a respiratory quotient of one corresponds to the oxidation of pure carbohydrate, and extreme diabetics oxidize fat in preference to carbohydrate, and may have a quotient just a little above 0.7. The results of Brown's and Burr's experiments could be interpreted to mean that the polyunsaturated fats not only lower the metabolic rate, but especially interfere with the metabolism of sugars. In other words, they suggest that the normal diet is diabetogenic.

During the six months of the experiment, the unsaturation of Brown's serum lipids decreased. The authors reported that "There was no essential change in the serum cholesterol as a result of the change in diet." However, in November and December, two months before the experiment began, it had been 252 mg.% in two measurements. At the beginning of the test, it was 298, two weeks later, 228, and four months later, 206 mg%. The total quantity of lipids in his blood didn't seem to change much, since the triglycerides increased as the cholesterol decreased.

By the time of Brown's experiment, other researchers had demonstrated that the cholesterol level was increased in hypothyroidism, and decreased as thyroid function, and oxygen consumption, increased. If Burr's team had been reading the medical literature, they would have understood the relation between Brown's increased metabolic rate and decreased cholesterol level. But they did record the facts, which is valuable.

The authors wrote that "The most interesting subjective effect of the 'fat-free' regimen was the definite disappearance of a feeling of fatigue at the end of the day's work."

A lowered metabolic rate and energy production is a common feature of aging and most degenerative diseases. From the beginning of an animal's life, sugars are the primary source of energy, and with maturation and aging there is a shift toward replacing sugar oxidation with fat oxidation. Old people are able to metabolize fat at the same rate as younger people, but their overall metabolic rate is lower, because they are unable to oxidize sugar at the same high rate as young people. Fat people have a similar selectively reduced ability to oxidize sugar.

Stress and starvation lead to a relative reliance on the fats stored in the tissues, and the mobilization of these as circulating free fatty acids contributes to a slowing of metabolism and a shift away from the use of glucose for energy. This is adaptive in the short term, since relatively little glucose is stored in the tissues (as glycogen), and the proteins making up the body would be rapidly consumed for energy, if it were not for the reduced energy demands resulting from the effects of the free fatty acids.

One of the points at which fatty acids suppress the use of glucose is at the point at which it is

converted into fructose, in the process of glycolysis. When fructose is available, it can by-pass this barrier to the use of glucose, and continue to provide pyruvic acid for continuing oxidative metabolism, and if the mitochondria themselves aren't providing sufficient energy, it can leave the cell as lactate, allowing continuing glycolytic energy production. In the brain, this can sustain life in an emergency.

Many people lately have been told, as part of a campaign to explain the high incidence of fatty liver degeneration in the US, supposedly resulting from eating too much sugar, that fructose can be metabolized only by the liver. The liver does have the highest capacity for metabolizing fructose, but the other organs do metabolize it.

If fructose can by-pass the fatty acids' inhibition of glucose metabolism, to be oxidized when glucose can't, and if the metabolism of diabetes involves the oxidation of fatty acids instead of glucose, then we would expect there to be less than the normal amount of fructose in the serum of diabetics, although their defining trait is the presence of an increased amount of glucose. According to Osuagwu and Madumere (2008), that is the case. If a fructose deficiency exists in diabetes, then it is appropriate to supplement it in the diet.

Besides being one of the forms of sugar involved in ordinary energy production, interchangeable with glucose, fructose has some special functions, that aren't as well performed by glucose. It is the main sugar involved in reproduction, in the seminal fluid and intrauterine fluid, and in the developing fetus. After these crucial stages of life are past, glucose becomes the primary molecular source of energy, except when the system is under stress. It has been suggested (Jauniaux, et al., 2005) that the predominance of fructose rather than glucose in the embryo's environment helps to maintain ATP and the oxidative state (cellular redox potential) during development in the low-oxygen environment. The placenta turns glucose from the mother's blood into fructose, and the fructose in the mother's blood can pass through into the fetus, and although glucose can move back from the fetus into the mother's blood, fructose is unable to move in that direction, so a high concentration is maintained in the fluids around the fetus.

The control of the redox potential is sometimes called the "redox signalling system," since it coherently affects all processes and conditions in the cell, including pH and hydrophobicity. For example, when a cell prepares to divide, the balance shifts strongly away from the oxidative condition, with increases in the ratios of NADH to NAD+, of GSH to GSSG, and of lactate to pyruvate. These same shifts occur during most kinds of stress.

In natural stress, decreased availability of oxygen or nutrients is often the key problem, and many poisons can produce similar interference with energy production, for example cyanide or carbon monoxide, which block the use of oxygen, or ethanol, which inhibits the oxidation of sugars, fats, and amino acids (Shelmet, et al., 1988).

When oxygen isn't constantly removing electrons from cells (being chemically reduced by them) those electrons will react elsewhere, creating free radicals (including activated oxygen) and reduced iron, that will create inappropriate chemical reactions (Niknahad, et al., 1995; MacAllister, et al., 2011).

Stresses and poisons of many different types, interfering with the normal flow of electrons to oxygen, produce large amounts of free radicals, which can spread structural and chemical damage, involving all systems of the cell. Ethyl alcohol is a common potentially toxic substance that can have this effect, causing oxidative damage by allowing an excess of electrons to accumulate in the cell, shifting the cells' balance away from the stable oxidized state.

Fructose has been known for many years to accelerate the oxidation of ethanol (by about 80%). Oxygen consumption in the presence of ethanol is increased by fructose more than by glucose (Thieden and Lundquist, 1967). Besides removing the alcohol from the body more quickly, it prevents the oxidative damage, by maintaining or restoring the cell's redox balance, the relatively oxidized state of the NADH/NAD+, lactate/pyruvate, and GSH/GSSG systems. Although glucose has this stabilizing, pro-oxidative function in many situations, this is a general feature of fructose, sometimes allowing it

to have the opposite effect of glucose on the cell's redox state. It seems to be largely this generalized shift of the cell's redox state towards oxidation that is behind the ability of a small amount of fructose to catalyze the more rapid oxidation of a large amount of glucose.

Besides protecting against the reductive stresses, fructose can also protect against the oxidative stress of increased hydrogen peroxide (Spasojevic, et al., 2009). Its metabolite, fructose 1,6-bisphosphate, is even more effective as an antioxidant.

Keeping the metabolic rate high has many benefits, including the rapid renewal of cells and their components, such as cholesterol and other lipids, and proteins, which are always susceptible to damage from oxidants, but the high metabolic rate also tends to keep the redox system in the proper balance, reducing the rate of oxidative damage.

Endotoxin absorbed from the intestine is one of the ubiquitous stresses that tends to cause free radical damage. Fructose, probably more than glucose, is protective against damage from endotoxin.

Many stressors cause capillary leakage, allowing albumin and other blood components to enter extracellular spaces or to be lost in the urine, and this is a feature of diabetes, obesity, and a variety of inflammatory and degenerative diseases including Alzheimer's disease (Szekanecz and Koch, 2008; Ujiie, et al., 2003). Although the mechanism isn't understood, fructose supports capillary integrity; fructose feeding for 4 and 8 weeks caused a 56% and 51% reduction in capillary leakage, respectively (Chakir, et al., 1998; Plante, et al., 2003).

The ability of the mitochondria to oxidize pyruvic acid and glucose is characteristically lost to some degree in cancer. When this oxidation fails, the disturbed redox balance of the cell will usually lead to the cell's death, but if it can survive, this balance favors growth and cell division, rather than differentiated function. This was Otto Warburg's discovery, that was rejected by official medicine for 75 years.

Cancer researchers have become interested in this enzyme system that controls the oxidation of pyruvic acid (and thus sugar) by the mitochondria, since these enzymes are crucially defective in cancer cells (and also in diabetes). The chemical DCA, dichloroacetate, is effective against a variety of cancers, and it acts by reactivating the enzymes that oxidize pyruvic acid. Thyroid hormone, insulin, and fructose also activate these enzymes. These are the enzymes that are inactivated by excessive exposure to fatty acids, and that are involved in the progressive replacement of sugar oxidation by fat oxidation, during stress and aging, and in degenerative diseases; for example, a process that inactivates the energy-producing pyruvate dehydrogenase in Alzheimer's disease has been identified (Ishiguro, 1998). Niacinamide, by lowering free fatty acids and regulating the redox system, supporting sugar oxidation, is useful in the whole spectrum of metabolic degenerative diseases.

A few times in the last 80 years, people (starting with Nasonov) have recognized that the hydrophobicity of a cell changes with its degree of excitation, and with its energy level. Recently, even in non-living physical-chemical systems, hydrophobicity and redox potential have been seen to vary together and to influence each other. Recent work shows how the oxidation of fatty acids contributes to the dissolution of mitochondria (Macchioni, et al., 2010). At first glance it might seem odd that the presence of fatty material could reduce the "fat loving" (lipophilic, equivalent to hydrophobic) property of a cell, but the fat used as fuel is in the form of fatty acids, which are soap-like, and spontaneously introduce "wetness" into the relatively water-resistant cell substance. The presence of fatty acids, impairing the last oxidative stage of respiration, increases the tendency of the mitochondrion to release its cytochrome c into the cell in a reduced form, leading to the apoptotic death of the cell. The oxidized form of the cytochrome is more hydrophobic, and stable.

Burr didn't understand that it was his rats' high sugar diet, freed of the anti-oxidative unsaturated fatty acids, that caused their extremely high metabolic rate, but since that time many experiments have made it clear that it is specifically the fructose component of sucrose that is protective against the antimetabolic fats.

Although Brown, et al., weren't focusing on the biological effects of sugar, their results are important in the history of sugar research because their work was done before the culture had been influenced by the development of the lipid theory of heart disease, and the later idea that fructose is responsible for increasing the blood lipids.

In 1963 and 1964, experiments (Carroll, 1964) showed that the effects of glucose and fructose were radically affected by the type of fat in the diet. Although 0.6% of calories as polyunsaturated fat prevents the appearance of the Mead acid (which is considered to indicate a deficiency of essential fats) the "high fructose" diets consistently add 10% or more corn oil or other highly unsaturated fat to the diet. These large quantities of PUFA aren't necessary to prevent a deficiency, but they are needed to obscure the beneficial effects of fructose.

Many studies have found that sucrose is less fattening than starch or glucose, that is, that more calories can be consumed without gaining weight. During exercise, the addition of fructose to glucose increases the oxidation of carbohydrate by about 50% (Jentjens and Jeukendrup, 2005). In another experiment, rats were fed either sucrose or Coca-Cola and Purina chow, and were allowed to eat as much as they wanted (Bukowiecki, et al, 1983). They consumed 50% more calories without gaining extra weight, relative to the standard diet. Ruzzin, et al. (2005) observed rats given a 10.5% or 35% sucrose solution, or water, and observed that the sucrose increased their energy consumption by about 15% without increasing weight gain. Macor, et al. (1990) found that glucose caused a smaller increase in metabolic rate in obese people than in normal weight people, but that fructose increased their metabolic rate as much as it did that of the normal weight people. Tappy, et al. (1993) saw a similar increase in heat production in obese people, relative to the effect of glucose. Brundin, et al. (1993) compared the effects of glucose and fructose in healthy people, and saw a greater oxygen consumption with fructose, and also an increase in the temperature of the blood, and a greater increase in carbon dioxide production.

These metabolic effects have led several groups to recommend the use of fructose for treating shock, the stress of surgery, or infection (e.g., Adolph, et al., 1995).

The commonly recommended alternative to sugar in the diet is starch, but many studies show that it produces all of the effects that are commonly ascribed to sucrose and fructose, for example hyperglycemia (Villaume, et al., 1984) and increased weight gain. The addition of fructose to glucose "can markedly reduce hyperglycemia during intraportal glucose infusion by increasing net hepatic glucose uptake even when insulin secretion is compromised" (Shiota, et al., 2005). "Fructose appears most effective in those normal individuals who have the poorest glucose tolerance" (Moore, et al., 2000).

Lipid peroxidation is involved in the degenerative diseases, and many publications argue that fructose increases it, despite the fact that it can increase the production of uric acid, which is a major component of our endogenous antioxidant system (e.g., Waring, et al., 2003). When rats were fed for 8 weeks on a diet with 18% fructose and 11% saturated fatty acids, the content of polyunsatured fats in the blood decreased, as they had in the Brown, et al., experiment, and their total antioxidant status was increased (Girard, et al., 2005). When stroke-prone spontaneously hypertensive rats were given 60% fructose, superoxide dismutase in their liver was increased, and the authors suggest that this "may constitute an early protective mechanism" (Brosnan and Carkner, 2008). When people were given a 300 calorie drink containing glucose, or fructose, or orange juice, those receiving the glucose had a large increase in oxidative and inflammatory stress (reactive oxygen species, and NF-kappaB binding), and those changes were absent in those receiving the fructose or orange juice (Ghanim, et al., 2007).

One of the observations in Brown, et al., was that the level of phosphate in the serum decreased during the experimental diet. Several later studies show that fructose increases the excretion of phosphate in the urine, while decreasing the level in the serum. However, a common opinion is that it's only the phosphorylation of fructose, increasing the amount in cells, that causes the decrease in the serum; that could account for the momentary drop in serum phosphate during a fructose load,

but--since there is only so much phosphate that can be bound to intracellular fructose--it can't account for the chronic depression of the serum phosphate on a continuing diet of fructose or sucrose.

There are many reasons to think that a slight reduction of serum phosphate would be beneficial. It has been suggested that eating fruit is protective against prostate cancer, by lowering serum phosphate (Kapur, 2000). The aging suppressing gene discovered in 1997, named after the Greek life-promoting goddess Klotho, suppresses the reabsorption of phosphate by the kidney (which is also a function of the parathyroid hormone), and inhibits the formation of the activated form of vitamin D, opposing the effect of the parathyroid hormone. In the absence of the gene, serum phosphate is high, and the animal ages and dies prematurely. In humans, in recent years a very close association has been has been documented between increased phosphate levels, within the normal range, and increased risk of cardiovascular disease. Serum phosphate is increased in people with osteoporosis (Gallagher, et al., 1980), and various treatments that lower serum phosphate improve bone mineralization, with the retention of calcium phosphate (Batista, et al., 2010; Kelly, et al., 1967; Parfitt, 1965; Kim, et al., 2003).

At high altitude, or when taking a carbonic anhydrase inhibitor, there is more carbon dioxide in the blood, and the serum phosphate is lower; sucrose and fructose increase the respiratory quotient and carbon dioxide production, and this is probably a factor in lowering the serum phosphate.

Fructose affects the body's ability to retain other nutrients, including magnesium, copper, calcium, and other minerals. Comparing diets with 20% of the calories from fructose or from cornstarch, Holbrook, et al. (1989) concluded "The results indicate that dietary fructose enhances mineral balance." Ordinarily, things (such as thyroid and vitamin D) which improve the retention of magnesium and other nutrients are considered good, but the fructose mythology allows researchers to conclude, after finding an increased magnesium balance, with either 4% or 20% of energy from fructose (compared to cornstarch, bread, and rice), "that dietary fructose adversely affects macromineral homeostasis in humans." (Milne and Nielsen, 2000).

Another study compared the effects of a diet with plain water, or water containing 13% glucose, or sucrose, or fructose, or high fructose corn syrup on the properties of rats' bones: Bone mineral density and mineral content, and bone strength, and mineral balance. The largest differences were between animals drinking the glucose and the fructose solutions. The rats getting the glucose had reduced phosphorus in their bones, and more calcium in their urine, than the rats that got fructose. "The results suggested that glucose rather than fructose exerted more deleterious effects on mineral balance and bone" (Tsanzi, et al., 2008).

An older experiment compared two groups with an otherwise well balanced diet, lacking vitamin D, containing either 68% starch or 68% sucrose. A third group got the starch diet, but with added vitamin D. The rats on the vitamin D deficient starch diet had very low levels of calcium in their blood, and the calcium content of their bones was low, exactly what is expected with the vitamin D deficiency. However, the rats on the sucrose diet, also vitamin D deficient, had normal levels of calcium in their blood. The sucrose, unlike the starch, maintained calcium homeostasis. A radioactive calcium tracer showed normal uptake by the bone, and also apparently normal bone development, although their bones were lighter than those receiving vitamin D.

People have told me that when they looked for articles on fructose in PubMed they couldn't find anything except articles about its bad effects. There are two reasons for that. PubMed, like the earlier Index Medicus, represents the material in the National Library of Medicine, and is a medical, rather than a scientific, database, and there is a large amount of important research that it ignores. And because of the authoritarian and conformist nature of the medical profession, when a researcher observes something that is contrary to majority opinion, the title of the publication is unlikely to focus on that. In too many articles in medical journals, the title and conclusions positively misrepresent the data reported in the article.

When the idea of "glycemic index" was being popularized by dietitians, it was already known that starch, consisting of chains of glucose molecules, had a much higher index than fructose and sucrose. The more rapid appearance of glucose in the blood stimulates more insulin, and insulin stimulates fat synthesis, when there is more glucose than can be oxidized immediately. If starch or glucose is eaten at the same time as polyunsaturated fats, which inhibit its oxidation, it will produce more fat. Many animal experiments show this, even when they are intending to show the dangers of fructose and sucrose.

For example (Thresher, et al., 2000), rats were fed diets with 68% carbohydrate, 12% fat (corn oil), and 20% protein. In one group the carbohydrate was starch (cornstarch and maltodextrin, with a glucose equivalence of 10%), and in other groups it was either 68% sucrose, or 34% fructose and 34% glucose, or 34% fructose and 34% starch. (An interesting oddity, fasting triglycerides were highest in the fructose+starch group.)

The weight of their fat pads (epididymal, retroperitoneal, and mesenteric) was greatest in the fructose+starch group, and **least in the sucrose group.** The starch group's fat was intermediate in weight between those of the sucrose and the fructose+glucose groups.

At the beginning of the experimental diet, the average weight of the animals was 213.1 grams. After five weeks, the animals in the fructose+glucose group gained 164 grams, those in the sucrose group gained 177 grams, and those in the starch group gained 199.2 grams. The animals ate as much of the diet as they wanted, and those in the sucrose group ate the least.

The purpose of their study was to see whether fructose causes "glucose intolerance" and "insulin resistance." Since insulin stimulates appetite (Chance, et al, 1986; Dulloo and Girardier, 1989; Czech, 1988; DiBattista, 1983; Sonoda, 1983; Godbole and York, 1978), and fat synthesis, the reduced food consumption and reduced weight gain show that fructose was protecting against these potentially harmful effects of insulin.

Much of the current concern about the dangers of fructose is focussed on the cornstarch-derived high fructose corn syrup, HFCS. Many studies assume that its composition is nearly all fructose and glucose. However, Wahjudi, et al. (2010) analyzed samples of it before and after hydrolyzing it in acid, to break down other carbohydrates present in it. They found that the carbohydrate content was several times higher than the listed values. "The underestimation of carbohydrate content in beverages may be a contributing factor in the development of obesity in children," and it's especially interesting that so much of it is present in the form of starch-like materials.

Many people are claiming that fructose consumption has increased greatly in the last 30 or 40 years, and that this is responsible for the epidemic of obesity and diabetes. According to the USDA Economic Research Service, the 2007 calorie consumption as flour and cereal products increased 3% from 1970, while added sugar calories decreased 1%. Calories from meats, eggs, and nuts decreased 4%, from dairy foods decreased 3%, and calories from added fats increased 7%. The percentage of calories from fruits and vegetables stayed the same. The average person consumed 603 calories per day more in 2007 than in 1970. If changes in the national diet are responsible for the increase of obesity, diabetes, and the diseases associated with them, then it would seem that the increased consumption of fat and starch is responsible, and that would be consistent with the known effects of starches and polyunsaturated fats.

In monkeys living in the wild, when their diet is mainly fruit, their cortisol is low, and it rises when they eat a diet with less sugar (Behie, et al., 2010). Sucrose consumption lowers ACTH, the main pituitary stress hormone (Klement, et al., 2009; Ulrich-Lai, et al., 2007), and stress promotes increased sugar and fat consumption (Pecoraro, et al., 2004). If animals' adrenal glands are removed, so that they lack the adrenal steroids, they choose to consume more sucrose (Laugero, et al., 2001). Stress seems to be perceived as a need for sugar. In the absence of sucrose, satisfying this need with starch and fat is more likely to lead to obesity.

The glucocorticoid hormones inhibit the metabolism of sugar. Sugar is essential for brain development and maintenance. The effects of environmental stimulation and deprivation-stress can be detected in the thickness of the brain cortex

in as little as 4 days in growing rats (Diamond, et al., 1976). These effects can persist through a lifetime, and are even passed on transgenerationally. Experimental evidence shows that polyunsaturated (omega-3) fats retard fetal brain development, and that sugar promotes it. These facts argue against some of the currently popular ideas of the evolution of the human brain based on ancestral diets of fish or meat, which only matters as far as those anthropological theories are used to argue against fruits and other sugars in the present diet.

Honey has been used therapeutically for thousands of years, and recently there has been some research documenting a variety of uses, including treatment of ulcers and colitis, and other inflammatory conditions. Obesity increases mediators of inflammation, including the C-reactive protein (CRP) and homocysteine. Honey, which contains free fructose and free glucose, lowers CRP and homocysteine, as well as triglycerides, glucose, and cholesterol, while it increased insulin more than sucrose did (Al-Waili, 2004). Hypoglycemia intensifies inflammatory reactions, and insulin can reduce inflammation if sugar is available. Obesity, like diabetes, seems to involve a cellular energy deficiency, resulting from the inability to metabolize sugar.

Sucrose (and sometimes honey) is increasingly being used to reduce pain in newborns, for minor things such as injections (Guala, et al., 2001; Okan, et al., 2007; Anand, et al., 2005; Schoen and Fischell, 1991). It's also effective in adults. It acts by influencing a variety of nerve systems, and also reduces stress. Insulin is probably involved in sugar analgesia, as it is in inflammation, since it promotes entry of endorphins into the brain (Witt, et al., 2000).

An extracellular phosphorylated fructose metabolite, diphosphoglycerate, has an essential regulatory effect in the blood; another fructose metabolite, fructose diphosphate, can reduce mast cell histamine release and protect against oxidative and hypoxic injury and endotoxic shock, and it reduces the expression of the inflammation mediators TNF-alpha, IL-6, nitric oxide synthase, and the activation of NF-kappaB, among other protective effects, and its therapeutic value is known, but its relation to dietary sugars hasn't been investigated.

A daily diet that includes two quarts of milk and a quart of orange juice provides enough fructose and other sugars for general resistance to stress, but larger amounts of fruit juice, honey, or other sugars can protect against increased stress, and can reverse some of the established degenerative conditions.

Refined granulated sugar is extremely pure, but it lacks all of the essential nutrients, so it should be considered as a temporary therapeutic material, or as an occasional substitute when good fruit isn't available, or when available honey is allergenic.

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Ray Peat's Newsletter

Independence - is loyalty to one's best self and principles, and this is often disloyalty to the general idols and fetishes. Mark Twain

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Fats, functions & malfunctions

Around the beginning of the 20th century, it was commonly believed that aging resulted from the accumulation of insoluble metabolic by-products, sort of like the clinker ash in a coal furnace. Later, age pigment or lipofuscin, was proposed to be such a material. It is a brown pigment that generally increases with age, and its formation is increased by consumption of unsaturated fats, by vitamin E deficiency, by stress, and by exposure to excess estrogen. Although the pigment can contribute to the degenerative processes, aging involves much more than the accumulation of insoluble debris; aging increases the tendency to form the debris, as well as vice versa.

There is a growing recognition that a persistent increase of free fatty acids in the serum, which is seen in shock, heart failure, and aging, indicates a bad prognosis, but there is no generally recognized explanation for the fact that free fatty acids are harmful. I want to mention some evidence showing that it is the accumulation of polyunsaturated fats in the body that makes them harmful.

The physical and functional properties of saturated fatty acids and polyunsaturated fatty acids (PUFA) are as different from each other as day is from night. The different fatty acids are directly involved, very often with opposite effects, in cell division and growth, cell stability and dissolution, the organization of cells, tissues, and organs, the regulation of pituitary hormones, adrenalin and sympathetic nervous activation, histamine and serotonin synthesis, adrenal cortex hormones, thyroid hormones, testosterone, estrogen, activators of the immune system and inflammation (cytokines), autoimmune diseases, detoxification, obesity, diabetes, puberty, epilepsy, Parkinson's disease, other degenerative nerve diseases and Alzheimer's disease, cancer, heart failure, atherosclerosis, and strokes. In each of these situations, the PUFA have harmful effects.

Most people are surprised to hear about the systematically harmful effects of the common

Saturated fatty acids terminate the stress reactions, polyunsaturated fatty acids amplify them.

dietary polyunsaturated fats and the protective effects of saturated fats. That's because there is a pervasive mythology of fats in our culture. Officials are proposing to tax saturated fats. Laws are being passed prescribing the fats that can be served in restaurants, and people write letters to editors about them, and great amounts of money are spent publicizing the importance of eating the right fats. Their focus is on obesity, atherosclerosis, and heart disease. The details of the myth change a little, as new fat products and industries appear.

As I understand the basic myth, the difference between the "essential" polyunsaturated fats and the saturated fats has to do with their shape---the unsaturated fatty acids bend or fold in a way that makes them more mobile than saturated fats of the same length, and this causes the all-important "membranes" of cells to be more fluid, and thus to have "better functions," though the myth isn't very clear on the issue of fluidity and functionality. At that point, it passes responsibility to the more fundamental biological myth, of the metabolically active cell membrane.

Practically everyone learns, in grade school and from television, about the good and the bad oils, and cell membranes, but it might seem likely that people who spend their lives investigating the role of fats in organisms would have acquired a

different, more complicated, view. But one of the most famous food fat researchers, J.M. Bourre, has succinctly (and thoughtlessly) expressed his understanding of the function of fatty substances in the body: "In fact the brain, after adipose tissue, is the organ richest in lipids, whose only role is to participate in membrane structure." (J.M. Bourre, 2004.) The fact that his editor let him publish the statement shows how the myth functions, causing people to accept things because they are "common knowledge." The influence of the medical and pharmaceutical industries is so pervasive that it becomes the context for most biological research.

The most highly unsaturated fats, including DHA, accumulate with aging, and their toxic fragments are increased in Alzheimer's disease.

Luckily, many people are working outside the myth, in specialized problems of physiology and cell biology, and their observations are showing a reality much more complex and interesting than the mythology.

When we eat more protein or carbohydrate than we need, the excess can be converted to fats, to be stored (as triglycerides), but even on a maintenance diet we synthesize some fats that are essential parts of all of our cells, including a great variety of phospholipids. People seldom talk about the importance of fats in the nucleus of the cell, but every nucleus contains a variety of lipids--phospholipids, sphingolipids, cholesterol, even triglycerides--similar to those that are found elsewhere in the cell and in every part of the body, including the brain (Balint and Holczinger, 1978; Irvine, 2002). Phospholipids are often considered to be "membrane lipids," but they have been demonstrated in association with elements of the cell's skeleton, involved in cell division, rather than in membranes (Shogomori, et al., 1993).

The cytoskeleton, a fibrous framework of the cell that's responsible for maintaining the organized structure of the cell, internal movement of organelles, coordination, locomotion, and cell division, is made up of three main kinds of protein, and all of these are affected differently by different kinds of fat.

Actions of lipids on the cell skeleton can change cells' movements, migrations, and invasiveness. Unsaturated fats cause clumping of some types of cell filament, condensation and polymerization of other types, in ways that are associated with brain degenerative diseases and cancer. For example, DHA alters the structure of the protein alpha-synuclein, causing it to take the form seen in Parkinson's disease and other brain conditions. The synucleins regulate various structural proteins, and are affected by stress, aging, and estrogen exposure, as well as by the polyunsaturated fats. One type of synuclein is involved in the promotion of breast cancer. Saturated fatty acids have exactly the opposite effects of PUFA on the synucleins, reversing the polymerization caused by the PUFA (Sharon, et al., 2003).

When cancers are metastasizing, their phospholipids contain less stearic acid than the less malignant tumors (Bougnoux, et al., 1992), patients with advanced cancer had less stearic acid in their red blood cells (Persad, et al., 1990), and adding stearic acid to their food delayed the development of cancer in mice (Bennett, 1984). The degree of saturation of the body's fatty acids corresponds to resistance to several types of cancer that have been studied (Hawley and Gordon, 1976; Singh, et al., 1995).

The phospholipids are being discussed in relation to drugs that can modify "signaling" by acting on phospholipid receptors, using language that was developed in relation to hormones. A surface barrier membrane, with receptors that send signals to the nucleus, is invoked by many of the recent discussions of phospholipids. There's no question that the fats do affect regulatory processes, but the theory and the language should correspond to the physiological and ecological realities. Vernadski's metaphor, that an organism is a "whirlwind of atoms," is probably more appropriate than "targeted signals and receptors" for understanding the physiology of fatty acids and phospholipids. The rate of change and renewal of these structural fats is very high. In rats, one study found a 30% decrease in the total phospholipid pool in the brain in the first 30 minutes after death (Adineh, et al., 2004). Another study in the brains of living rats found that a particular class of brain

lipids, ethanolamine plasmalogens, had a turnover time of about 5 hours (Masuzawa, et al., 1984). (This type of lipid is an important component of the lipoproteins secreted by the liver into the serum [Vance, 1990], and is also a major lipid in the heart and brain.) Stresses such as the loss of sleep cause great distortions in phospholipid metabolism throughout the body, especially in the brain and liver.

Actions of lipids on the cell skeleton can be seen, even in short term experiments. The effects of the "essential fatty acid" linoleic acid have been compared to the drug colchicine, which is known to interfere with the cell skeleton and cell division. According to Hoover, et al., (1981), it disturbed the structure of the cytoskeleton more than colchicine does; it caused the cell filaments to clump together, while saturated fatty acids didn't have such an effect.

The fatty molecules that participate in the normal cell functions are made by cells even when they are grown in a fat-free solution in a culture dish. They include saturated fatty acids such as palmitate and stearate, and omega-9 unsaturated fats, such as oleic acid and omega-9 polyunsaturated fatty acids. The saturated fatty acids found in the nucleus associated with the chromosomes are resistant to change when the composition of the animal's diet changes (Awad and Spector, 1976), while the unsaturated fats change according to the diet. These intracellular fats are essential for cell division and the regulation of the genes, and for cell survival (Irvine, 2002). Although cells make the saturated fats that participate in those basic functions, the high rate of metabolism means that some of the lipids will quickly reflect in their structure the free fatty acids that circulate in the blood. The fats in the blood reflect the individual's diet history, but recently eaten fats can appear in the serum as free fatty acids, if the liver isn't able to convert them into triglycerides.

The polyunsaturated fatty acids differ from the saturated fats in many ways, besides their shape and their melting temperature, and each type of fatty acid is unique in its combination of properties. The polyunsaturated fatty acids, made by plants (in the case of fish oils, they are made by algae), are less stable than the saturated fats, and the omega-3 and omega-6 fats derived from them, are very susceptible to breaking down into toxins, especially in warm-blooded animals. Other differences between saturated and polyunsaturated fats are in their effects on surfaces (as surfactant), charges (dielectric effects), acidity, and their solubility in water relative to their solubility in oil. The polyunsaturated fatty acids are many times more water soluble than saturated fatty acids of the same length. This property probably explains why only palmitic acid functions as a surfactant in the lungs, allowing the air sacs to stay open, while unsaturated fats cause lung edema and respiratory failure.

The great difference in water/oil solubility affects the strength of binding between a fatty acid and the lipophilic, oil-like, parts of proteins. When a protein has a region with a high affinity for lipids that contain double bonds, polyunsaturated fatty acids will displace saturated fats, and they can sometimes displace hormones containing multiple double bonds, such as thyroxine and estrogen, from the proteins that have a high specificity for those hormones. Transthyretin (also called prealbumin) is important as a carrier of the thyroid hormone and vitamin A. The unsaturation of vitamin A and of thyroxin allows them to bind firmly with transthyretin and certain other proteins, but the unsaturated fatty acids are able to displace them, with an efficiency that increases with the number of double bonds, from linoleic (with two double bonds) through DHA (with six double bonds).

The large amount of albumin in the blood is important in normal fatty acid binding and transport, but it is also an important part of our detoxifying system, since it can carry absorbed toxins from the intestine, lungs, or skin to the liver, for detoxification. Albumin facilitates the uptake of saturated fatty acids by cells of various types (Paris, et al., 1978), and its ability to bind fatty acids can protect cells to some extent from the unsaturated fatty acids (e.g., Rhoads, et al., 1983). The liver's detoxification system processes some polyunsaturated fats for excretion, along with hormones and environmental toxins.

The movement of proteins from the plasma into cells has often been denied, but there is clear

evidence that a variety of proteins, including IgG, transferrin haptoglobin, and albumin can be found in a variety of cells, even in the brain (Liu, et al., 1989). Cells are lipophilic, and absorb molecules in proportion to their fattiness; this long ago led people to theorize that cells are coated with a fat membrane.

The idea of a semipermeable membrane, similar in function to the membrane inside an egg shell, was proposed about 150 years ago, to explain the ability of living cells to concentrate certain chemicals, such as potassium ions, while excluding others, such as sodium ions. This idea of a molecular sieve was shown to be invalid when radioactive isotopes made it possible to observe that sodium ions diffuse freely into cells, and it was replaced by the idea of a metabolically active membrane, containing "pumps" that made up for the inability to exclude various things, and that allowed cells to retain high concentrations of some dissolved substances that are free to diffuse out of the cell. The general idea of the membrane as a barrier persisted as a sort of "common sense" idea, that has made people ignore experiments that show that some large molecules, including some proteins, can quickly and massively enter cells. Albumin and transthyretin are two proteins that are sometimes found in large quantities inside cells, and their primary importance is that they bind and transport biologically active oily molecules.

While the competition by PUFA for protein binding sites blocks the effects of thyroid hormone and vitamin A, the action of PUFA on the sex steroid binding protein (SBP, or SSBG, for sex steroid binding globulin) increases the activity of estrogen. That's because the SSBG neutralizes estrogen by binding it, keeping it out of cells; free PUFA keep it from binding estrogen (Reed, et al., 1986). People with low SSBG/estrogen ratio have an increased risk of cancer. When the SSBG protein is free of estrogen, it is able to enter cells, and in that estrogen-free state it probably serves a similar protective function, capturing estrogen molecules that enter cells before they can act on other proteins or chromosomes. Transthyretin, the main transporter of thyroid and vitamin A, and albumin (which can also transport thyroid hormone) are both able to enter cells, while loaded with thyroid hormone and vitamin A. Albumin becomes more lipophilic as it binds more lipid molecules, so its tendency to enter cells increases in proportion to its fat burden. Albumin in the urine is a problem associated with diabetes and kidney disease; albumin loaded with fatty acids passes from the blood into the urine more easily than unloaded albumin, and it is the fatty acids, not the albumin, which cause the kidney damage (Kamijo, et al., 2002). It's possible that SSBG's opposite behavior, entering cells only when it carries no hormones, is the result of becoming less lipophilic when it's loaded with estrogen.

Since most people believe that cells are enclosed within a barrier membrane, a new industry has appeared to sell special products to "target" or "deliver" proteins into cells across the barrier. Combining anything with fat makes it more likely to enter cells. Stress (which increases free fatty acids and lowers cell energy) makes cells more permeable, admitting a broader range of substances, including those that are less lipophilic.

Linoleic acid and arachidonic acid, which are said to "make the lipid membrane more permeable," in fact make the whole cell more permeable, by binding to the structural proteins throughout the cell, increasing their affinity for water, causing generalized swelling, as well as mitochondrial swelling (leading to reduced oxidative function or disintegration), allowing more calcium to enter the cell, activating excitatory processes, stimulating a redox shift away from oxidation and toward inflammation, leading to either (inappropriate) growth or death of the cell.

When we don't eat for many hours, our glycogen stores decrease, and adrenaline secretion is increased, liberating more glucose as long as glycogen is available, but also liberating fatty acids from the fatty tissues. When the diet has chronically contained more polyunsaturated fats than can be oxidized immediately or detoxified by the liver, the fat stores will contain a disproportionate amount of them, since fat cells preferentially oxidize saturated fats for their own energy, and the greater water solubility of the PUFA causes them to be preferentially released into the bloodstream during stress.

In good health, especially in children, the stress hormones are produced only in the amount needed, because of negative feedback from the free saturated fatty acids, which inhibit the production of adrenalin and adrenal steroids, and eating protein and carbohydrate will quickly end the stress. But when the fat stores contain mainly PUFA, the free fatty acids in the serum will be mostly linoleic acid and arachidonic acid, and smaller amounts of other unsaturated fatty acids. These PUFA stimulate the stress hormones, ACTH, cortisol, adrenaline, glucagon, and prolactin, which increase lipolysis, producing more fatty acids in a vicious circle. In the relative absence of PUFA, the stress reaction is self limiting, but under the influence of PUFA, the stress response becomes self-amplifying.

When stress is very intense, as in trauma or sepsis, the reaction of liberating fatty acids can become dangerously counter-productive, producing the state of shock. In shock, the liberation of free fatty acids interferes with the use of glucose for energy and causes cells to take up water and calcium (depleting blood volume and reducing circulation) and to leak ATP, enzymes, and other cell contents (Boudreault and Grygorczyk, 2008; Wolfe, et al., 1983; Selzner, et al, 2004; van der Wijk, 2003), in something like a systemic inflammatory state (Fabiano, et al., 2008) often leading to death.

The remarkable resistance of "essential fatty acid deficient" animals to shock (Cook, et al., 1981; Li et al., 1990; Autore, et al., 1994) shows that the polyunsaturated fats are centrally involved in the maladaptive reactions of shock. The cellular changes that occur in shock--calcium retention, leakiness, reduced energy production--are seen in aging and the degenerative diseases; the stress hormones and free fatty acids tend to be chronically higher in old age, and an outstanding feature of old age is the reduced ability to tolerate stress and to recover from injuries.

Despite the instability of polyunsaturated fatty acids, which tend to break down into toxic fragments, and despite their tendency to be preferentially liberated from fat cells during stress, the proportion of them in many tissues increases with age (Laganiere and Yu, 1993, 1987; Lee, et al., 1999; Smidova, et al., 1990; Tamburini, et al., 2004; Nourooz-Zadeh J and Pereira, 1999). This progressive increase with age can be seen already in early childhood (Guerra, et al., 2007). The reason for this increase seems to be that the saturated fatty acids are preferentially oxidized by many types of cell, (fat cells can slowly oxidize fat for their own energy maintenance). Albumin preferentially delivers saturated fatty acids into actively metabolizing cells such at the heart (Paris, 1978) for use as fuel. This preferential oxidation would explain Hans Selye's results, in which canola oil in the diet caused the death of heart cells, but when the animals received stearic acid in addition to the canola oil, their hearts showed no sign of damage.

The most highly unsaturated fats found in fish oil break down into chemicals that block the use of glucose and oxygen.

Since healthy cells are very lipophilic, saturated fatty acids would have a greater tendency to enter them than the more water soluble polyunsaturated fats, especially those with 4, 5, or 6 double bonds, but as cells become chronically stressed they more easily admit the unsaturated fats, which slow oxidative metabolism and create free radical damage. The free radicals are an effect of stress and aging, as well as a factor in its progression.

When stress signals activate enzymes in fat cells to release free fatty acids from the stored triglycerides, the enzymes in the cytoplasm act on the surface of the droplet of fat. This means that the fatty acids with the greatest water solubility will be liberated from the fat to move into the blood stream, while the more oil soluble fatty acids will remain in the droplet. The long chain of saturated carbon atoms (8 in the case of oleic acid, 15 in palmitic acid, and 17 in stearic acid) in the "tail" of oleic, palmitic, and stearic acid will be buried in the fat droplet, while the tail of the n-3 fatty acids, with only 2 saturated carbons, will be the most exposed to the lipolytic enzymes. This means that the n-3 fatty acids are the first to be liberated during stress, the n-6 fatty acids next. Saturated and monounsaturated fatty acids are

selectively retained by fat cells (Speake, et al., 1997).

Women are known to have a greater susceptibility than men to lipolysis, with higher levels of free fatty acids in the serum and liver, because of the effects of estrogen and related hormones.

Women on average have more DHA circulating in the serum than men (Giltay, et al., 2004; McNamara, et al., 2008; Childs, et al., 2008). This highly unsaturated fatty acid is the first to be liberated from the fat stores under stress, and, biologically, the meaning of estrogen is to mimic stress. Estrogen and polyunsaturated fatty acids have similar actions on cells, increasing their water content and calcium uptake. Long before the Women's Health Initiative reported in 2002 that the use of estrogen increased the risk of dementia, it was known that the incidence of Alzhemer's disease was 2 or 3 times higher in women than in men. Men with Alzheimer's disease have higher levels of estrogen than normal men (Geerlings, et al., 2006). The amount of DHA in the brain (and other tissues) increases with aging, and its breakdown products, including neuroprostanes, are associated with dementia. Higher levels of DHA and total PUFA are found in the plasma of demented patients (Laurin, et al., 2003).

Another interesting association of the highly unsaturated fats and estrogen in relation to brain function is that DHA increases the entry of estrogen into the pregnant uterus, but inhibits the entry of progesterone (Benassayag, et al., 1999), which is crucial for brain cell growth. When Dirix, et al., (2009) supplemented pregnant women with PUFA, they found that fetal memory was impaired.

The crucial mitochondrial respiratory enzyme, cytochrome c oxidase, declines with aging (Paradies, et al., 1997), as the lipid cardiolipin declines, and the enzyme's activity can be restored to the level of young animals by adding cardiolipin. The composition of cardiolipin changes with aging, "specifically an increase in highly unsaturated fatty acids" (Lee, et al., 2006). Other lipids, such as a phosphatidylcholine containing two myristic acid groups, can support the enzyme's activity (Hoch, 1992). Even supplementing old animals with hydrogenated peanut oil restores mitochondrial respiration to about 80% of normal (Bronnikov, et al., 2010). Supplementing thyroid hormone increases mitochondrial cardiolipin (Paradies and Ruggiero, 1988). Eliminating the polyunsaturated fats from the diet increases mitochondrial respiration (Rafael, et al., 1984).

The ratio of saturated fatty acids to polyunsaturated fatty acids is decreased in cancer. Omega-3 fats promote metastasis.

Excitotoxicity is the process in which activation of a nerve cell beyond its capacity to produce energy injures or kills the cell, by increasing intracellular calcium. Glutamic acid and aspartic acid are the normal neurotransmitter excitatory amino acids. Estrogen increases the activity of the excitatory transmitter glutamate (Weiland, 1992), and glutamate increases the release of free fatty acids (Kolko, et al., 1996). DHA (more strongly even than arachidonic acid) inhibits the uptake of the excitotoxic amino acid aspartate, and in some situations glutamate, prolonging their actions. Thymocytes are much more easily killed by stress than nerve cells, and they are easy to study. The PUFA kill them by increasing their intracellular calcium. The toxicity of DHA is greater than that of EPA, whose toxicity is greater than alpha-linolenic acid, and linoleic acid was the most potent (Prasad, et al., 2010). Excitotoxicity is probably an important factor in Alzheimer's disease (Danysz and Parsons, 2003).

When the brain is injured, DHA and arachidonic acid contribute to brain edema, weakening the blood-brain-barrier, increasing protein breakdown, inflammation, and peroxidation, while a similar amount of stearic acid in the same situation caused no harm (Yang, et al., 2007). In other situations, such as the important intestinal barrier, EPA and DHA also greatly increased the permeability (Dombrowsky, et al., 2011).

The process by which excitotoxicity kills a cell is probably a foreshortened version of the aging process.

Excitotoxins (including endotoxin) increase the formation of neuroprostanes and isoprostanes (from n-3 and n-6 PUFA) (Milatovic, et al., 2005), and acrolein and other fragments, which inhibit the use of glucose and oxygen. DHA and EPA

produce acrolein and HHE, which react with lysine groups in proteins, and modify nucleic acids, changing the bases in DNA.

Increased intracellular calcium activates lipolysis (by phospholipases), producing more free fatty acids, as well as excitation and protein breakdown, and in the brain neurodegenerative diseases, calcium excess contributes to the clumping of synuclein (Wojda, et al., 2008), an important regulator of the cytoskeletal proteins. The reduced function of normal synuclein makes cells more susceptible to excitotoxicity (Leng and Chuang, 2006).

If the cells adapt to the increased calcium, rather than dying, their sensitivity is reduced. This is probably involved in the "defensive inhibition" seen in many types of cell. In the brain, DHA and arachidonic acid "brought the cells to a new steady state of a moderately elevated [intracellular calcium] level, where the cells became virtually insensitive to external stimuli. This new steady state can be considered as a mechanism of self-protection" (Sergeeva, et al., 2005). In the heart, the PUFAs decreased the sensitivity to stimulation (Coronel et al., 2007) and conduction velocity (Tselentakis, et al., 2006; Dhein, et al., 2005). Both DHA and EPA inhibit calcium-ATPase (which keeps intracellular calcium low to allow normal neurotransmission) in the cerebral cortex; this suggests "a mechanism that explains the dampening effect of omega-3 fatty acids on neuronal activity" (Kearns and Haag, 2002).

In normal aging, most processes are slowed, including nerve conduction velocity, and conduction velocity in the heart (Dhein and Hammerath, 2001). A similar "dampening" or desensitization is seen in sensory, endocrine, and immune systems, as well as in energy metabolism. Calorie restriction, by decreasing the age-related accumulation of PUFA (20:4, 22:4, and 22:5), can prevent the decrease of sensitivity, for example in lymphoid cells (Laganier and Fernandes, 1991). The known effects of the unsaturated fats on the organizational framework of the cell are consistent with the changes that occur in aging.

One of the essential protective functions that declinę with aging is the liver's ability to detoxify chemicals, by combining them with glucuronic acid, making them water soluble so that they can be excreted in the urine. The liver (and also the intestine and stomach) efficiently process DHA by glucuronidation (Little, et al., 2002). Oleic acid, one of the fats that we synthesize ourselves, increases (about 8-fold) the activity of the glucuronidation process (Krcmery and Zakim, 1993; Okamura, et al., 2006). However, this system is inhibited by the PUFA, arachidonic acid (Yamashita, et al., 1997), and also by linoleic acid (Tsoutsikos, et al., 2004), in one of the processes that contribute to the accumulation of PUFA with aging.

Animals that naturally have a relatively low level of the highly unsaturated fats in their tissues have the greatest longevity. For example, the naked mole rate has a life expectancy of more than 28 years, about 9 times as long as other rodents of a similar size. Only about 2% to 6% of its phospholipids contain DHA, while about 27% to 57% of the phospholipids of mice contain DHA (Mitchell, et al., 2007).

The famously long-lived people of Azerbaijan eat a diet containing a low ratio of unsaturated to saturated fats, emphasizing fruits, vegetables, and dairy products (Grigorov, et al., 1991).

Some of the clearest evidence of the protective effects of saturated fats has been published by A.A. Nanji's group, showing that they can reverse the inflammation, necrosis, and fibrosis of alcoholic liver disease, even with continued alcohol consumption, while fish oil and other unsaturated fats exacerbate the problem (Nanji, et al., 2001). Glycine protects against fat accumulation in alcohol-induced liver injury (Senthilkumar, et al., 2003), suggesting that dietary gelatin would complement the protective effects of saturated fats.

The least stable n-3 fats which accumulate with age and gradually reduce energy production also have their short term effects on endurance. Endurance was much lower in rats fed a high n-3 fat diet, and the effect persisted even after 6 weeks on a standard diet (Ayre and Hulbert, 1997). Analogous, but less extreme effects are seen even in salmon, which showed increased oxidative stress on a high n-3 diet (DHA or EPA), and

lower mitochondrial cytochrome oxidase activity (Kjaer, et al., 2008).

Maintaining a high rate of oxidative metabolism, without calorie restriction, retards the accumulation of PUFA, and a high metabolic rate is associated with longevity. An adequate amount of sugar maintains both a high rate of metabolism, and a high respiratory quotient, i.e., high production of carbon dioxide. Mole rats, bats, and queen bees, with an unusually great longevity, are chronically exposed to high levels of carbon dioxide. Carbon dioxide forms carbamino bonds with the amino groups of proteins, inhibiting their reaction with the reactive "glycating" fragments of PUFA.

To minimize the accumulation of the highly unsaturated fatty acids with aging, it's probably reasonable to reduce the amount of them directly consumed in foods, such as fish, but since they are made in our own tissues from the "essential fatty acids," linoleic and linolenic acids, it's more important to minimize the consumption of those (from plants, pork, and poultry, for example).

In the resting state, muscles consume mainly fats, so maintaining relatively large muscles is important for preventing the accumulation of fats.

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Ray Peat's Newsletter

Heraclitus: Unless you expect the unexpected you will never find truth, for it is hard to discover and hard to attain.

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Physiology texts and the real world

Hospital accidents kill more people than highway accidents. But when people die while they are receiving standard, but irrational and antiscientific treatments and "support," the deaths aren't counted as accidents. The numbers are large.

Medical training and medical textbooks bear great responsibility for those unnecessary deaths. Most medical research is done under the influence of mistaken assumptions, and so fails to correct the myths of medical training. If the "consumers" or victims of medicine are willing to demand concrete justifications before accepting "standard procedures," they will create an atmosphere in which medical mythology will be a little harder to sustain.

A sentence taken out of context is likely to be misleading. A chemical equation that is concerned only with the reactants, catalyst, and product, can be misleading, and its industrial application is likely to produce devastation and pollution along with the intended product. In nature and industry, the reactants, products, and energy changes are linked to the ecology and to the economy. In physiological chemistry, events in the organism are linked to the environment so closely that food, water, air, soil, and pollution form a firmly linked functional system.

But "medical physiology" has evolved as a separate thing, in which formulas that describe specific situations are linked to each other by fragmentary schemes, terminology, and computer models. This jerrybuilt scheme is even more roughly set into a hypothetical environment of "the origin of life," "evolution," "inheritance," "society," and a few other perfunctory contextualizations that have no more relevance to the subject than do the literary epigraphs that are often used at the beginning of chapters in medical books, to signify that the author isn't just a technical hack.

This physiological mythology has made possible a practice of medicine in which "genes" and "a virus" are regularly invoked to explain things that can't be remedied, and in which any fleshy body is described as "well nourished," and in which malnutrition and poisoning by pollutants are systematically dismissed as explanations for sicknesses, while thousands of different drugs are administered according to instructions given by their salesmen. It is also deeply linked to attitudes that have turned the practice of medicine into the surest way for an individual to get rich and retire early. It creates a sense of confidence that the physician is doing the right thing, because there is a little physiological rationale for everything. ***When a practice is replaced by its opposite, there is also a rationale for that.*** In fact, medical textbooks are written to rationalize the highly arbitrary practices of the industry. If, for some reason, perpetual motion machines had been as successful economically as steam engines were, laws of thermodynamics would have been written to describe them, just as thermodynamic laws were invented to describe the theory of steam engines.

It was odd and interesting when a vice presidential candidate stepped to the podium several years ago and asked "who am I? What am I doing here?" But those questions are really of the greatest importance and interest, and physiology should be an attempt to understand more fully what we are, what we are doing, and how we are doing it. When we have comprehensive answers to those questions, then we will be in a position to

create systematically valid solutions for our problems.

For physiology, the equivalent of medicine's "first do no harm" would be "first, don't believe unfounded doctrines." Accepting that principle puts a person into a critical attitude, and experiments can become actually "empirical," an extension of experience that allows you to perceive new things, rather than "testing hypotheses." Unless a hypothesis is a generalization from real experience, rather than a deduction from a doctrine, progress is likely to be very slow. A first step in developing a critical attitude is to identify the idols that stand in the way of real understanding.

Immunity, intelligence, appetites, tumor growth, aging, the proper development of organs—everything that we think of as the biological foundations of health and sickness—will be misinterpreted if there are fundamental misconceptions about physiology.

Physiology is the study of the vital functions of organisms, but especially when talking about "pathologic physiology," great emphasis in physiology textbooks is given to the processes that maintain homeostasis of the *milieu interieur,* or the constancy of composition of the "fluid in which tissue cells are bathed." Since cells are embedded in a gel-like matrix, "connective tissue," the connective tissue should have some serious attention in physiology courses, but in practice its composition is described, and then the rest of physiology treats it as the "extracellular space." Only specialists in the extracellular matrix are likely to take it seriously as a factor in physiology.

If medical physiologists are likely to think of cells as being "bathed in fluid" which fills the empty spaces around the cells, they are also likely to think of the cell's interior as a watery solution which "fills the space enclosed by the cell membrane." It is this image of the organism that has made traditional biochemistry possible, since enzymes extracted from cells and dissolved in water had been thought to function the way they function in the living state. But the living cell isn't like a tiny water-filled test-tube.

Some of the points that should be considered in a realistic (and therefore coherent) physiology text:

Connective tissues, ground substance—making a multicell organism--secreting the right amount, modifying/maintaining it, responding to the scaffolding--where the crucial *milieu interieur* is.

Cellular energy, a structural idea—a finely organized catalyst, a readiness for work, and conditions that determine the equilibrium of reactions.

The dimensions of the organism range from cellular fields to organismic intentions, via functional systems.

Physiology should be understood in terms of its geochemical setting, because otherwise basic definitions will be built up in the belief that life is discontinuous from its physical environment, separated by membranes, and maintained by the expense of energy mainly to preserve gradients across those membranes; while in actuality the chemical energy released by living substance is spent in renewing structures, and the gradients are mainly passive physical-chemical consequences of structure. The spontaneous polymerization that occurs under volcanic conditions creates substances with intrinsic functions. The living state is a substance that is always being renewed as it interacts with its environment, and from the larger persepective, it is an evolving catalyst that modifies the environment so that the whole system approaches equilibrium with the energy that flows through it. Since the evolving system stores energy in its structure, the cosmic energy sources and sinks are at the boundaries of the system, and are the only questions that (so far) transcend the issue of life in its environment. The chemistry of the planet is tied up with cosmic energy, but the nature of the system as a whole is still relatively unexplored. If plants are bracketed by the sun, carbon dioxide and water, animals are bracketed by sugar and oxygen.

Acid-base regulation--selectivity; physical chemistry of coral, bone; kidney, lung; roles of oxygen, carbon dioxide and protein.

An Arrhenius base is something which produces hydroxide ions when it's dissolved in water.

Metal, an element that forms a base by combining with a hydroxyl group (or groups).

Base, an electropositive element (cation) that combines with an anion to form a salt; a compound ionizing to yield hydroxyl ion.

Electropositive atoms tend to lose electrons.

Electronegative atoms, such as oxygen, chlorine, and fluorine, tend to take up an electron and to become negatively ionized.

Definitions of Arrhenius and Lewis for acids and bases. It's important to keep both sides of an ionizable compound in mind, and to pay more attention to electrons than to protons.

A Lewis acid is an electron acceptor.

Alkali reserve, (Stedman's phrase:) "the basic ions, mainly the bicarbonates" (bicarbonates of this or that; there is no abstract "bicarbonate.")

Carbon dioxide is a neutral Lewis acid, that associates with the hydroxide ion. (This observation may be shocking to people who have thought too long in terms of abstract "bicarbonate.")

Carbon dioxide regulates water, minerals, energy and cellular stability, excitation, and efficiency.

Cellular respiration regulates both energy and substance disposition.

Respiration regulates osmotic/oncotic pressure, including the hydration (and dehydration) of the extracellular matrix.

Electrons, positive charges, electronegativity, and induction: The unity of metabolism and signalling interactions; hormones are physical-chemical agents, not information carriers. Electrets, piezoelectricity, and crystal/bond stresses are relevant to physiology; the behavior of ionic materials in bulk water provides misleading images for physiology. Space charges are more relevant to physiology than fluxes in ion channels.

Inductive effect: an electronic effect transmitted through bonds in an organic compound due to the electronegativity of substituents.

Cooperative adsorption interacts with inductive effects producing coherent, systemic changes and stabilities.

Steroids, peptides, biogenic amines, and other things considered as hormones and transmitters, are active as modifiers of ***adsorption, induction, and metabolic pathways.*** Their structural effects create, or inhibit, phase transitions in cells. Synergies of radiation, estrogen, and hypoxia are intelligible in terms of phase instability.

Alkaloids: organic substances occurring naturally, which are basic, forming salts with acids. The basic group is usually an amino function.

The disposition of electrons in cells and tissues is a global phenomenon, integrating metabolism, pH, osmolarity, and sensitivity. ***Excitation creates a field of alkalinity.***

Cellular differentiation; developmental fields, polarities.

Regulation of water; electroosmosis; edema in relation to cellular energy.

Vicinal water, all water near surfaces, most of the water in cells, has special properties.

Needs on the cellular level guide the organism's adaptations.

Functional systems, multilevel adaptive integrations, in which many "systems" and cell types are organized according to activity and needs, leading to anatomical and functional changes.

Energy and relaxation, cellular inhibition, a structural state involving the entire cell substance. High energy phosphate bonds explain nothing about the cell's energy.

Multilevel self-regulation; cell intelligence, organic compensations (function producing structure, organ regeneration, vascular neogenesis, stem cell functions, immunity/morphogenesis, tubercles/tumors, fat/fiber/muscle/phagocytosis) permits highly organized and novel adaptive responses, which are goal-directed rather than mechanistically "programmed" from the genes.

Sensitivity and motility—plants and animals, subtle cues, rhythms, motivations.

Adaptation—learning, intention, and stress.

Light, energy, motion; pigments and electron donor-acceptor bonds.

Acceptor of action, innate and learned models of reality. Intentionality is involved in "reflexes."

Digestion—bowel and liver; immune system and nervous system; **need** and intepretation, analysis; approximation and assimilation. Intestinal flora and detoxifying. Detoxifying fatty acids, estrogen, insulin, nerve chemicals, etc.

Nutrition—appetite and satisfaction.

Reproduction, puberty, menopause; how they are affected by the environment.

Humor, curiosity, exploratory and inventive potentials and need.

Growth and aging; energy, individualization and generalization; mitosis and meiosis, germ cells.

Nurse cells, their interactions in various organs.

Chalones, wound hormones, phagocytes, regeneration, nerve products; inhibition of growth by nerves. Frog extracts in development. Anatomy is a dynamic system, whose integration is part of physiology.

Inflammations and tumors are systemic events, in causes and effects.

Inflammation, edema, fibrosis, calcification, and atrophy--the basic pathology.

Organisms relate to the biosphere as factors in the creation of new equilibria.

Between 1947 and 1956, Arthur C. Guyton, of Ole Miss, wrote a textbook of medical physiology, and one of his students, J. E. Hall, has added chapters to it. It is the most widely used physiology textbook in the world. It may be more influential than the bible, since it has shaped the behavior of millions of doctors, affecting billions of people. Its success probably has something to do with Guyton's unusual personal experience. After graduating from Harvard Medical School and, along with others from Harvard, working in germ warfare,* he contracted polio, and returned to Mississippi. As someone moving from the centers of excellence and power to the most backward state in the nation, instead of using textbooks he wrote handouts for the classes he taught there, devising what he thought were plausible explanations for everything in physiology. A personalized perspective and desire to keep things simple made the book, based on those handouts, readable and popular.

The circulatory system, and the movement of fluids in the body, are at the center of physiology, so it is of interest that Guyton believed that, in the "spaces around cells," there is a negative pressure, a partial vacuum, that sucks fluid out of the capillaries. He believed that this suction would balance a column of 5 or 10 mm of mercury. The rib cage, and the force of the diaphragm muscle, can maintain a negative pressure around the lungs, preventing their elastic collapse, but there is no such shell around the rest of the body; if elastic fibers of connective tissue could be anchored to such a shell, then such a suction/vacuum would be conceivable.

Hydrostatic and osmotic pressures interact in tissues, but even the hydrostatic forces produced by the heartbeat are known only approximately, as estimates, on the microscopic level. The belief in subatmospheric interstitial pressure is unreasonable on its face, and measurements are so inaccurate in the microcirculation that its disproof would be somewhat like proving that fairies aren't responsible for the Brownian motions seen under a microscope.

The oncotic/osmotic behavior of proteins in the blood and extracellular (the term ***interstitial*** implies the presence of empty spaces which aren't really there) fluid is usually, in medical physiology, assumed to be a fixed quantity determined by the nature of the polymer. Swelling and syneresis (contraction) of gels, with the absorption or release of water, are strongly influenced by the electrical properties of the system, which includes solvent water, bound water, and small solutes and ions as well as the polymers. Changes in pH and ionic strength and temperature, and the presence of solutes modifying the polymer's affinity for water, affect the osmotic behavior of the polymer, and of gels formed by such polymers. Since the extracellular spaces are mainly filled with solid gels, Guyton's image of simple fluids entering and leaving these "spaces" reveals a major conceptual error, and that error has been widely propagated

by medical professors. If a person imagines open spaces, interstices, between cells, then the question of the fluid pressure in these chambers seems reasonable, and the factors that produce edema will be thought of mechanically. But if we call the material between cells the "extracellular matrix," and recognize its relatively solid gel nature, we will see the problem of edema in physical-chemical terms, rather than as a problem of simple hydraulics.

[*Biographical side-lights: Guyton graduated from Ole Miss in 1939, got his medical degree from Harvard in 1943, where the department of bacteriology had a grant to study the polio virus, and where he worked with people "involved in the war effort," and then from 1944 to 1946 was involved in germ warfare research, mainly at Camp Detrick. Camp Detrick had been established as the center for chemical and biological warfare research, and a test site was established in Mississippi in 1943. Guyton's first paper was on aerosol research (published in 1946), and studies at that time were being done to improve the spreading of germs in aerosols. Bacterial aerosols were tested on the public in San Francisco, in 1950. Guyton's Harvard colleagues established a polio research lab at Children's Hospital Medical Center. When he left the navy, after working at Camp Detrick, Guyton resumed work at Mass General, and contracted polio before he finished his residency.]

Idols of medical physiology, foundations and cornerstones for the landfill, some things you shouldn't know about physiology:

Genes control the cell, the organism is its genome, the nucleus regulates the cytoplasm. Information flowing from the genes produces and maintains the organism.

Acquired traits aren't passed on; mutations are random, the genome doesn't acquire information from the organism or environment, the germ-line is isolated.

Physiology is bounded by the informational function of genes.

The cell is a drop of water containing dissolved chemicals enclosed in a membrane.

Random diffusion governs energy metabolism, gene induction, and other intracellular events.

Enzyme reactions occur when dissolved molecules randomly diffusing come into contact with a suitable enzyme, as described by the Michaelis-Menton equation.

The Donnan equilibrium explains cellular electrical behavior, and since ions are distributed across the membrane by active transport, the membrane potential is maintained by the expense of metabolic energy.

Water is just a peculiar solvent.

Water structure changes only at extremes of temperature.

Cells are perfect osmometers.

There are empty spaces between cells.

The membrane regulates the composition of the cytoplasm, with pumps and pores and channels. Cells must produce enough energy to keep the pumps running.

Membrane receptors regulate cell responses.

Cells are activated by receptors, and physical forces for which there are no receptors have no effect on cells except when they are above a threshold at which they cause discrete chemical changes.

The nervous system is hard-wired.

Brain and heart cells don't regenerate.

There is an immune system, whose function is to destroy pathogens, with inflammation as one of its functions, and its specific reactions are determined by the selection of clones which were generated by random mutations; an autonomic nervous system, which regulates visceral reflexes by innervating, via receptors, smooth muscle, heart muscle, and glands; an endocrine system, regulated mainly by negative feedback, that produces hormone molecules that carry messages to the receptors in certain target tissues.

Inflammation is produced by germs, and is a defensive reaction of the immune system, and so is good. (Sterile inflammation is too confusing to include within the ambit of medical physiology, since it is associated with serious harm to the organism. The roles in inflammation of the nervous and endocrine systems and kidneys and membrane pumps and osmoregulation aren't discussed in polite books.)

During development, cells are organized into systems, and they don't change their type. In the case of germ cells, their type is determined before they exist. Cells are able to undergo only about 50

divisions, and most of those divisions are used up in producing an adult organism.

The committed nature of the organism's cells and anatomy make radical functional adaptation impossible.

Hormones and transmitter substances act only through specific receptor molecules.

High energy phosphate bonds in compounds such as ATP provide energy to molecular pumps and motors.

Molecular forces act only locally.

Pathologies are primarily local: Inflammations and tumors have local causes, and their effects are local. Specific and local treatments are ideal. Circulation is treated as a plumbing problem, tumors as clones of defective cells.

Consciousness is produced by nervous signals that transmit information, and can be compared with the handling of information by computers.

Excitation and inhibition are functions of cell membranes.

Artificial intelligence research into computational and nerve net systems is as much a part of research into the physiology of consciousness as computer modeling of feedback systems is a form of research into endocrine physiology and immunology.

Estrogen, testosterone, thyroid, prolactin, serotonin, adrenalin, prostaglandins, etc., are carriers of information in an informational system.

Cyclic functions and behaviors are governed by genes.

The existence of hard-wired informational receptor systems and gene-induction systems is necessary because of the random diffusional nature of the other cellular processes and materials.

Essentially, an organism consists of random inert matter given form and activity by the imposition of genetic information accumulated through random mutations.

(There are really people who still believe those things.)

A NOTE ON SCIENTIFIC REVOLUTIONS:

If scientific revolutions depended on "the authorities," then the Copernican revolution would be dated from the Pope's apology. The fact that the major journals are controlled by antiscientific dimwits helps to define where science exists. Gilbert Ling's revolution in cell physiology has been moved along by the existence of the journal, Physiological Chemistry and Physics (and medical NMR).

Michael Polanyi, in ***Personal Knowledge,*** maybe even more than Thomas Kuhn did in his famous book (*Structure of Scientific Revolutions*), helped to solidify the belief that there is a real international monolithic "community of science." Even though Polanyi, working "in isolation" in Hungary created his general and elegant adsorption isotherm, he didn't teach it to his own students, because of his belief in that community of science, which ridiculed his work because it wasn't based on their (false) assumptions about the electrical nature of matter.

The linguistic and cultural isolation of Hungary and Russia from Europe has permitted them to evolve distinctive scientific cultures. C.C. Lindegren, in Cold War in Biology, showed that political forces in the U.S. and England suppressed anti-Mendelian ideas by identifying them as subversive, imposing the Central Dogma of genetics. But even within an authoritarian national tradition, there are little communities of science, where the real development of thought can take place.

Perceptions that are clear and useful are the real revolutions in science, and the rest of it has to do with social and financial commitments.

Even in the short time since Kuhn wrote his book, the status of medicine has changed significantly, putting it right up with militarism and the energy industry as a source of political and economic power. The authoritarian monolith that has been known as the community of science has become increasingly (even in areas such as astronomy, where commercial interests aren't so crudely involved) a structure of cultural propaganda maintained by bullying and fraud. Since the "normal science" in these authoritarian settings is dedicated to evading the truth, it becomes almost a guide to where to look for the truth. It's sort of analogous to the "mystery" of why breast cancer mortality is lowest in the poorest part of the U.S., Appalachia, and highest in the richest regions: the medical industry goes where the money is, taking death with it. Science, like health, thrives on the neglect of the corrupt industry.

I have always felt that the cybernetic definition of communication as the transfer of something that makes a difference should be applied to speech and writing. As a student and teacher, I saw that information which made a difference was the essence of intellectual excitement and growth. But making a difference is exactly what university administrators and journal editors don't want. ***

Letters to the Editor

The Foreskin is Necessary

Editor:

I wish to congratulate you on your excellent review of the issues surrounding infant circumcision in your April 1996 issue. I have not seen elsewhere such a thorough discussion in a format which provides both a provocative challenge to health professionals and presents information in a manner that is fully accessible to a layman.

James Ryan, MD, MPH
Harvard School of Public Health
Boston, Massachusetts, USA

Editor:

This letter concerns the routine surgery, circumcision, as there are no medical reasons for it. This practice of routine Newborn Infant Circumcision and Female Genital Mutilation need to be exposed for the fraud and atrocities that they both are. Normal and natural human genitals need no alterations or mutilations. It is worse than "Sexual Rape."

Neither I nor any of my male family members and friends have ever had any medical problems with our intact sex organs. To me, it is unbelievable that such "reasons" as hygiene, religion, or "matching Daddy" are actually being used to justify the destruction of a highly useful, normal, pleasure enhancing body part.

The majority of circumcisers are male physicians who were circumcised as infants. They cannot know the merits of the foreskin. These doctors, even the ones who don't do circumcisions, are ignorant of the natural penis. They are uneducated on the structure and function of the healthy foreskin.

My journey of becoming an activist against Human Genital Mutilation (HGM) started over 50 years ago and I'm still trying to have it abolished as a crime against children.

Everett Carlisle
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Octacosanol for Brain Injury

Editor:

In the May *Townsend Letter* Denise Brown asked if any readers might provide suggestions that might prove helpful to her husband who suffered a serious traumatic head injury which left him partially paralyzed.

One substance which has been advocated as being potentially helpful in such cases is octacosanol. I do not have any personal experience with octacosanol, but I did correspond for a period of some years with the well-known nutritionist, Carlton Fredericks, now unfortunately deceased. Carlton was a great advocate of the use of octacosanol. In his letter to me of September 17, 1981 he wrote: "I have seen responses to octacosanol therapy in cerebral palsy – particularly spastics; in post-viral encephalitis; post stroke syndrome, muscular dystrophy, multiple sclerosis, epilepsies following brain trauma, etc." He has also mentioned cases of carbon-monoxide poisoning and near-drowning.

In addition to sending me some of his own writings on the subject, Carlton sent me a bibliography of articles, some of which go back to the 1920s and 1930s.

My octacosanol file weighs almost 8 ounces. Any readers interested in having a copy made and mailed to them, may have one for $10, which will cover copying and postage charges.

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Concerns About Progesterone Cream and Yam Extracts

Editor:

I notice that on page 68 of the April issue a word was added editorially to "Preserving the tissues," a chapter from my book on the menopause, which reversed my meaning. In the 7th and 8th lines, it should say "and other factors, especially progesterone and thyroid, allowed the organism to restore itself in ways that neutralized the cortisone response," but as printed it has me saying "estrogen...called up...progesterone and thyroid, and allowed the organism to restore itself..." My original wording expressed the opposition between estrogen and the restorative factors, but your alteration has me seeming to side with those who claim therapeutic benefits for estrogen.

In spite of Dr. Gaby's good comments on the "yam scam," I notice you publish an ad for a "yam extract cream." If progesterone is "a yam extract," then so is estrogen, and so are the anabolic steroids, the glucocorticoids, and the contraceptive steroids: Does the phrase "Mexican yam root extract" or "wild yam" honestly describe the contents of the product? Obviously not, because Dioscorea, wild yam root, has been in the National Formulary for many years, as a drug in itself, used to treat "bilious colic" and as a diuretic and expectorant. In the last several years I have spoken to people in the Portland and Seattle offices of the FDA about this, as well as with people involved in the production of the "yam" creams, and it seems clear to me that the FDA is either knowingly condoning this fraudulent labeling, or actively participating in it. While they fail to enforce their laws regarding honest labeling, they have told me that I (rather than those who mislabel the products, and who have falsely used my name in their advertising) appear to be the one violating the law by writing about progesterone and related substances while having patents on them. It is clear to me that it is the scientific information which offends them, not the illegal claims and

mislabelings. It is only the latter over which they have jurisdiction, and it is there that they take no action.

If the yam-substance is applied to the skin, the saponins in it might be good for cleaning the skin (it was commonly used for washing clothes, shampooing, etc.), but they will have no hormone action. If the "menopause creams" contain estrogen, they might have a systemic effect, but the studies of topical progesterone, by Papa and Kligman, showed that progesterone had a local effect, but no detectable systemic effect. This is because of its low solubility in ordinary oils. The progesterone-vitamin E combination, which I patented, is stably dissolved so that it can be absorbed by any route – transdermal, oral, rectal, or vaginal, but I have not licensed my patent to any of the companies such as Yamcon/Phillips Nutritionals or Pro-Gest/Transitions/ Professional & Technical Services, which advertise creams for the treatment of menopause. Some creams contain progesterone, some creams contain vitamin E, some contain neither. The patented progesterone-in-vitamin E products are sold only in Eugene, Oregon.

The order in which ingredients are listed on the label must be in the order of their quantity in the product. Pro-Gest's advertisement claims that "For over 17 years, physicians have recommended Pro-Gest to their menopausal patients," but I participated in the design of some of the original progesterone lotions which were sold by Professional and Technical Services (while I was "President" of that corporation), and those early formulations (I still have copies of the various brand-name labels) essentially had no effective shelf life, because of their poor formulation; the progesterone was crystallized by the time it arrived from the factory. The composition of the various Professional & Technical Services products, at least according to their labels, has changed over the years. It is incorrect to say that Pro-Gest has existed for 17 years. One formulation, for example, showed a higher content of vitamin E than of progesterone, meaning that there was sufficient vitamin E to dissolve the progesterone, and thus to infringe my patent. When I pointed this out to MacFarland, he didn't want to pay me royalties, so he obligingly changed the formulation. "Cielo 2000" another of MacFarland's previous products, moved vitamin E far down on its label, meaning that its solvent action was very limited. My samples of Pro-Gest contain massive amounts of crystals, indicating that they didn't copy my patented composition.

A friend quoted one manufacturer of a progesterone cream, as saying, when she told him of my patent, "that's easy to get around." But a truthful label will say in a simple way whether or not it is violating my patent, by indicating the relative amounts of vitamin E and progesterone.

Lab analysis shows that the products licensed under my patent contain by far the largest amount of progesterone of any product tested, but the important point is that the progesterone is dissolved in vitamin E, and is completely available biologically. Crystalline progesterone isn't available transdermally, and when it is ingested, it is quickly metabolized by the bowel and the liver, into a derivative of progesterone, which has a certain biological activity, but which is chemically and biologically distinct from progesterone.

A small amount of any herbal saponin, such as those found in the Dioscorea yams, may be harmless, but larger amounts can be lethal, by causing hemolysis, and there is also some evidence that it can cause liver damage. The people in Mexico traditionally used the yam for washing clothes and for killing fish. Russell Marker, who created the steroid industry based on the Mexican yam, took a dose of saponin while working on a project in Mexico, and was seriously poisoned. His colleague, Norman Applezweig, said the next day that he looked as if he had "been hit by a truck," because he was covered by bruises resulting from the hemolytic action of the saponins.

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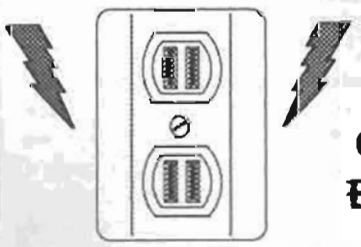

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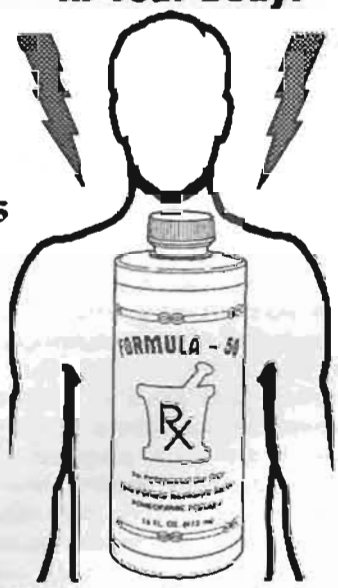

A number of years ago the noted soil and nutritional scientist Dr. G.H. Earp-Thomas said: "This is what happens in the blood at a time of crisis. Minerals are liberated and at that instant the invading germs are instantly killed. The reason for rapid killing, I believe, is the increased osmotic pressure brought about by the introduction of the minerals. Also, the electric potential from negative to higher positive charges are brought about. It is my belief that a potentiometer would show that effect, that a negative charge causes death as all dead people are acid and negative electically, whereas all living people are alkaline and positive. This I believe is a law of nature like gravity and is immutable. That being the case no person can be dead if they are alkaline and positively charged."

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Letters to the Editor

Critiquing "Dr. McDaniel Responds" Letter

Editor:

People have expressed concern to me about statements in the letter (June, 1996) from H. Reg McDaniel, Director of the Fisher Institute for Medical Research. Although it is headed "Dr. McDaniel Responds," the letter isn't responsive to Kenneth Sancier's questions, and even seems to further blur the "identity" issue that Sancier asked about. The editor describes McDaniel as a consultant for the company that markets "dioscorea." I don't know if that is accurate. Dozens, maybe hundreds, of people have asked me about a chart used in marketing Emprise products that indicates diosgenin is a precursor of DHEA. Although I can't imagine what enzymes might achieve that conversion, no one seems to want to say whether their products contain diosgenin or DHEA or yam tissue. If they contain yam tissue, then they should be discussing the issue of toxicity.

I don't doubt McDaniel's claim that the statements he makes "reflect the consensus of a research pharmacologist, biochemist, molecular biologist, gastroenterologist and gastrointestinal physiologist, as well as physicians who interpret scientific data...." While the editors of *JAMA* make similar claims about the authoritative nature of their publication, I noticed a completely idiotic statement about yams and steroids in that journal, indicating that the yams used by the steroid industry were the same as edible yams. (There are about 600 types of steroid-rich yam; a typical one looks like Bigfoot, weighs as much as 90 pounds, and is poisonous.)

McDaniel's group of specialists were asked to evaluate the set of articles cited in his letter. It would seem that neither McDaniel nor his professionals bothered to read the articles. Although none of McDaniels' sentences stands up to close scrutiny, let me comment on half of one of his sentences: [animals] "...were administered diosgenin and it was converted by the adrenals to pregnenolone and then to estrogen,[2] (3) oral diosgenin reversed experimental diabetes,[3] (4) oral diosgenin lowered blood cholesterol levels,[4] (5) diosgenin has also shown the capacity to induce megakaryocytic differentiation of bone marrow stem cells in tissue culture; a demonstration of hormonal regulatory influence at the cellular level expressed free of other sources of endocrine influence...."[5]

Far from saying that diosgenin is converted by the adrenals to pregnenolone and estrogen, Rao, et al., say it has not been ascertained whether it acts directly or by being metabolized. Their evidence argues against that, by "excluding any possibility of diosgenin having progesterone-like activity in mouse," since any pregnenolone produced would be far more likely to produce progesterone-like effects than estrogenic effects. A. Lipshutz's work made that clear.

Although I am not familiar with dioscoretine, and haven't read the paper by M.M. Iwu, et al., their abstract strongly suggests that it has nothing to do with diosgenin, because their hypoglycemic substance has an LD50 in mice of 0.58 g/kg, and diosgenin isn't likely to be that toxic. The paper by Iwu, et al., wasn't about "reversing diabetes," but only about the observation that dioscoretine lowered blood sugar after four hours in rabbits. Thousands of other seriously toxic substances can cause a sudden decrease in blood sugar.

McDaniel indicates that Malinow, et al., studied the effects of oral diosgenin on cholesterol, but, as their title says, they were examining digitonin, a toxin from a different family of plants. Since McDaniel brought up the subject by citing this digitonin study, I should mention that one of the effects seen by other researchers, with Dioscorea-derived compounds, is chronotropic heart stimulation, suggesting a parallel to digitalis.

Beneytout, et al., describe the HEL cells as a human erythroleukemia cell line, which isn't the same as McDaniel's description of them as "stem cells," and they compare the effect of diosgenin to that of phorbol myristate acetate treatment, and say nothing that could be construed as "a demonstration of hormonal regulatory influence at the cellular level expressed free of other sources of endocrine influence." Phorbol myristate esters are recognized as potent co-carcinogens. Both diosgenin and PMA caused an increase in the number of cells containing 4 or more nuclei. Diosgenin, we might conclude, is as effective as PMA in promoting abnormal development in cancer cells. This would suggest that diosgenin is something to be avoided.

If McDaniels gets paid for mentioning DHEA, pregnenolone, diosgenin, and dioscorea on the same page, he has done his job. But the *Townsend Letter*'s important forum for uncensored dialogue is abused when someone uses it repeatedly for evasive verbiage and misstatement of fact.

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Criticism and the Experts

The present government of the U.S. is talking about reforming the educational system and the health care system. It is clear that the insurance companies and other components of the medical establishment aren't going to be inconvenienced by the reforms. Teachers, on the other hand, are increasingly being made the scapegoats for our national decline. I want to propose that an orientation toward results, rather than procedures, is the essential reform that we need in both health care and education. The goals of both health care and education, I think, are to maximize abilities and pleasures, minimizing disabilities and displeasures. The World Health Organization has defined health in terms of decreasing dysadaptations, and improving our adaptation to our surroundings.

As Felix Meerson (described in my monograph "Resistance of the heart") has shown, the brain is the preferred organ of adaptation, because adaptation on the level of learning has no biological costs, in the sense of limiting our structure and function. As soon as we submit to a cultural stereotype or a textbook answer, we give up our creative capacity to adapt mentally, and begin to avoid problems, questions, and mysteries, because adaptation at any level other than creative imagination is a bodily stress; the acceptance of authority commits a person to wielding any authority they have, or helplessly adapting to the authority of others. Full health requires the responsible and creative use of the mind. This is why I think it is necessary to consider the reform of health care and education together, as a single project of cultural reform.

Certain things led me into a habit of doubting the experts. For example, in high school I had a state-certified biology teacher who refused to mention the word "evolution," an American history teacher who worshipped Hitler, and a "civics" teacher who told race jokes in class. Although it wasn't their apparent intention, they were contributing something to my education. In a graduate school seminar in American literature, I mentioned the relevance of social class to the work of some writer, and the professor interrupted to tell me that "there are no classes in the United States"; I explained that I didn't mean class or caste in the legally enforced sense that India and England have them, but social-economic classes. At that, every student in the seminar joined with the professor to make it clear that I couldn't go on with my discussion if I had to refer to the "non-existent" social classes. That same summer term, I was looking for a job at a community college, and just a few hours' drive from the great university I found myself in the midst of horrifying unimaginable squalor. My fellow students had grown up in that region, and had to know about those areas. They helped to make me aware that there are academic fetish-ideas. Later I would find that the sciences were just as susceptible to academic fetishes, but that the humanities had the advantage of a tradition that emphasizes critical judgement; while the sciences base undergraduate education heavily on textbooks, the humanities emphasize study of original materials.

Over a period of several years, I enrolled as a graduate student in seven other departments, and learned to orient myself to what I perceived as a general academic psychosis, with variations to suit the subject matter; no department, from art to zoology, was free from the crazy authoritarianism, but a small percentage of individuals in any discipline seemed able to avoid the dogmatic frenzy. Once, in the late 1960s, I tried to communicate my perception to students at the University of Oregon. I organized a course called "Interdepartmental Perspectives on the Nature of Man." We invited the most highly-thought-of professors from ten departments to lecture on "their discipline's special contribution to understanding human nature." We had professors from the sciences, social science, philosophy and religion, rhetoric, and folklore. Six weeks into the course, we had heard six professors deliver one or two-hour lectures on the central importance of Noam Chomsky's generative grammar for understanding the nature of man. After the sixth lecture, one of the students took me aside and said "You're playing a trick on us, aren't you?" Since I had emphasized that the professors should talk about their department's special contribution, I wasn't responsible for the embarrassing stereotypy of their lectures, but in fact, that student had understood my reason for organizing the class. In a later decade, "deconstructionism" might have been the specific content of the lectures, but the point would still be that the university curriculum consists largely of stylish, borderline-psychotic, garbage. (Seen from a certain viewpoint, that academic stuff seems neither trashy nor crazy, but rather elegant, noble, and relevant. You have to adopt that viewpoint to write an A paper; you have to discard that viewpoint to do something useful. The desire for useful knowledge leads to an attitude of active criticism.)

The academic sciences and humanities are similar in their fear of responsibility for knowledge. Everyone marches in step, assigns the right textbooks, and holds the acceptable assumptions, so that they can keep their job. Ultimately (and frequently enough to keep people in line) the board of trustees exercises its power to herd the university faculty in the desired direction.

Because of my own experiences as a critical student, in 1959 or 1960 I conceived of having a college whose teachers and students were the trustees. (We called it Blake College, for William Blake.) Responsibility would be institutionalized, to some extent. To keep students from feeling that they were leaving the real world when they entered the college, I proposed that it should grant degrees based on "recognized achievement," and I specifically suggested that the BA degree should require a score above the 87th percentile on the Graduate Record Examination, since this score alone should be enough to gain admittance to any good graduate program. In fact, private universities generally recognized that a GRE score higher than that of 87% of the graduates from recognized US colleges was a reasonable basis for graduate admission, but the state universities required that their applicants have degrees from "accredited institutions." (Our students all received their degrees, and their GRE scores averaged at the 95th percentile. A couple of our students had previously been ranked in the lowest 10% academically. A change of their feelings about knowledge changed their mental abilities.) The regional accrediting association told us that they would consider many factors, including the size of our endowment and whether we had a football team, and made it clear that they were a kind of mafia that wasn't sympathetic with our idea of

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requiring that every graduate have a high level of intellectual competence.

What this means is that competence is defined as a) enrolling in the institutions presently established by governmental authority; b) jumping through ten to forty hoops per year, for a certain number of years; the size and height of the hoops are set by the authorities in consultation with the experts; c) in certain cases, one or two flaming hoops may be required, to exalt the authority of the profession. Art Pearl, a professor of education, used to argue that students should be awarded their degrees when they enroll in college, since the degrees don't stand for any special competence now, and the recognition of that would make people think about the actual qualifications needed for doing a job. If we compare education to the rites of initiation many cultures have, then symbolizing entry into adulthood with a college degree, earned by a feat of endurance, isn't so strange, but the ritual could be modified so that it didn't interfere with learning the things people really want to learn.

After people have proven their obedience/compliance, by years of expensive subservience, then they may be allowed to take certain licensing exams. By law, these tests are not sufficient evidence of competence, and only those who hold accredited professional degrees may take them. If people without degrees were allowed to take the licensing exams, it might be discovered that the endurance-training had a detrimental effect on the students' problem-solving abilities. Several years ago, it was discovered that students' IQs decreased with each additional year they spent in certain schools. In a study of graduate students, it was found that there was an inverse relationship between their academic standing and their distance from the mean IQ, in either direction, that is, the mean IQ is excellent academically.

If we are concerned with what people know and are able to do, then we can find ways to help them develop the knowledge and ability that they want. However if that goal is a fraud, and we really want a nation of obedient, submissive, rigid and uncritical people who don't rock any boats, then we should just worry about keeping guns and drugs out of the schools (remember the math graduate student who murdered his professor?) and otherwise keep the educational system as it is, with emphasis on form, rather than outcome.

The idea of testing for competence (with varying degrees of generality, relating to specific tasks or ability to respond to novelty) would fundamentally change our educational institutions, but its influence would extend into the workplace. Many jobs would disappear if everyone's competency improved. In medicine, people talk about payment for keeping the patient well, instead of for alleviating or curing disease, but keeping the public healthy is going to require a major social effort to keep food, water, air, homes, travel and workplaces safe. If people become aware of their potential for creative adaptation and problem solving, the whole direction of the economy must change, because status and style-dependent consumption derive their importance from the absence of intrinsic interest in many of our activities.

Active criticism is an old idea that is close to "imaginative science." B.G. Niebuhr is considered to have founded German historiography with his concept of criticizing the source documents. Goethe used the phrase "tatige skepsis" (active doubt, constructive criticism) to describe Neibuhr's method. William Blake emphasized that criticism and imagination must be combined to correct error; doubt by itself is futile, imagination is vulnerable without organized and active criticism. More recently, Salvador Dali's concept of "critical paranoia" advocated the same intelligent use of the brain, to discover what is true, important, and interesting in ambiguous situations. Meerson, the investigator of stress physiology, speaks of adaptive culture as the first level of protection against harmful conditions.

For about 50 years, the concept "psychosomatic" has been trivialized to mean "it's just imaginary." But now, the studies of the physiology of helplessness show that a seemingly small difference in experience and attitude can cause a very great difference in the ability to mobilize biological energy and various aspects of immunity, such as Natural Killer cell activity. There is now general agreement on the distinction between the demobilized state of helplessness and the state of active adaptation. If everyone could be "vaccinated" against helplessness, there would be a general improvement in health and ability to learn. But irrational institutions keep making helpless people. A culture which promoted a responsible, creative use of critical intelligence would minimize the experience of helplessness; and at the same time it would shift our adaptive habits upward, toward seeking reasonable imaginative solutions to problems that now are often perceived as stresses and threats.

After my experience at Blake College, in which the essence of the institution was to support the inclination of students and teachers toward being responsible for knowledge, I found that it was often possible to reinterpret institutional rules to create a similar temporary environment within the existing conventional universities.

The greatest impediment to doing this is probably the fear of unemployment; subscribing to the current academic idiocy, or the current cliche of the marketplace, is felt to be necessary to fit in. In questions of health and education our culture is at a critical point. Things could be reinstitutionalized to give all power to the drug, insurance and communication industries, or they could begin to be de-institutionalized to expand the scope for intelligent individual activity.

Art Pearl's suggestion that students be automatically granted degrees can be seen as the student's equivalent of tenure. If teachers were much more secure about their jobs, there wouldn't be so much pressure to conform. There are foolish and wicked teachers, and good and wise teachers. If students know there are objective standards of achievement, they won't be under the teachers' power; teachers will be challenged by the needs and curiosities of the students. Students will necessarily become conscious of the need to examine and question the source of information. Little kids naturally have that inclination, which is the inclination of good scientists and artists.

The Japanese have relatively high levels of achievement in education. They also invented crawl-in hotel "rooms," stuffers to pack people into subways, and snap-on apartments. Their achievement comes at the price of exhaustion, misery, and diseases of stress. They represent one of our potential futures. The other potential future takes into account our health and happiness, and defines health as having the capacity for creative mental adaptation.

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Chronic Fatigue

by Ray Peat, Ph.D.
Ray Peat's Newsletter

A good thing about science is that even dull-witted people can make real contributions to knowledge, by working carefully and methodically. Science tolerates (but doesn't require) quite a bit of stupidity. But I am inclined to think that education (or training) in science is heavily biased toward stupidity. It is through education that the achievements of science become part of our culture, and our culture influences the future directions science will take. So, both science and our culture would be better off if we would habitually ask whether the scientist's basic assumptions are justified, what alternative explanations had been considered, exactly what is meant by a specific word, and so on. Such questions almost always reveal the most embarrassing weaknesses in a position that "almost everyone agrees is correct." In biology and medicine, it seems that nearly everyone explains almost everything with a few interlocking ideas: DNA, membranes, membrane pumps, membrane receptors and receptors for the DNA, and ion channels. A belief in the explanatory power of these ideas can convert an observation that bacteria behave a little oddly when they are given ethyl alcohol, into a publishable speculation on the "molecular biology of membranes."

When the cells of fat, or depressed, or tired people are found to be in a low energy state, defective membranes, or membrane pumps or membrane receptors are often mentioned. Since phospholipids, which contain fatty acids of various degrees of unsaturation, are believed to be a major component of "the membranes," some people argue that eating more of the polyunsaturated fats will help to build new membranes, or to increase the "fluidity" of the membranes. If it is suggested that the cells should be producing more energy, some people suggest that, since the "mitochondrial membranes" are highly unsaturated, eating more of the polyunsaturated fats will help them to produce more energy.

A crucial enzyme in the mitochondrion is cytochrome oxidase, which reacts directly with oxygen, completing (or beginning) the process of chemical respiration. It is this enzyme (which is most sensitive to cyanide) which appears to be a "choke point" for energy production in various situations. Learning how to preserve and promote the activity of this enzyme is an important issue for everything having to do with biological energy.

Mitochondria from animals which are fed a diet lacking the "essential" unsaturated fatty acids are more resistant to oxidation than the mitochondria from animals fed a standard diet containing unsaturated oils, but they also have very different in vitro swelling behavior. R. M. Johnson's investigations (*Exp. Cell Res.* 32, 118-127, 1963) suggested that "the swelling tendency in liver mitochondria...is associated with altered respiratory and/or phosphorylating mechanisms rather than with membrane alteration." Kunkel and Williams (*J. Biol. Chem.*, 1951) found that the very high respiratory rate of animals fed a diet lacking polyunsaturated fats was caused primarily by a great increase in the activity of cytochrome oxidase, and that adding an "essential fatty acid" strong inhibited this enzyme's activity. (Other interesting observations were that "endogenous" respiration was low in the oil-deficient animals with a high metabolic rate, and aerobic glycolysis failed to produce energy, while anaerobic glycolysis was normal. Warburg emphasized the importance of aerobic glycolysis in cancer metabolism. Anaerobic glycolysis occurs in healthy cells. Aerobic glycolysis – the kind which is typical of cancer – being energetically idle in these animals might relate to the known freedom from cancer of animals which do not receive unsaturated fats.)

Cytochrome oxidase contains both iron and copper, and the copper component is apparently responsible for the enzyme's absorption of red light. The copper's function isn't understood, but it is suspected to be involved in regulating the efficiency of respiration. A protein called metallothionein, which is induced by cortisol or heavy metals, also binds copper, and might be one of the ways in which stress and heavy metal poisoning can accelerate the process of aging and degeneration.

The similarity of the effects of cyanide and polyunsaturated fats on respiration, and on cytochrome oxidase, suggests the possibility that the "essential" fatty acids might, like cyanide, form a complex with the copper ion. Unsaturated compounds, especially unsaturated phospholipids, can form strong chelation complexes with copper.

While thyroid supplementation produces increased activity of cytochrome oxidase, the avoidance of unsaturated oils would probably, to a great extent, make thyroid supplementation unnecessary to maintain a high rate of health-supporting mitochondrial respiration. Pregnenolone often normalizes metabolism in a way that can make thyroid supplementation unnecessary, and part of its action is probably the result of stabilizing the mitochondria. Even cholesterol (which is converted to pregnenolone in the mitochondria) seems to have a stabilizing effect, since it inhibits oxidation of unsaturated fats.

B.L. Epel (*Photophysiology* vol. VIII, 1973, pp. 209-230), discusses the evidence showing that blue light inhibits respiration by inactivating cytochrome oxidase, and says "If it is conceded that this phenomenon is universal, it is then intuitively obvious that most organisms must possess a protective or active repair mechanism since sunlight appears to be directly detrimental to few organisms."

The many studies which show that red light promotes respiration probably explain the fact that the blue light in sunlight isn't very harmful, since the sun also contains red light, which would tend to reverse the damage done by the blue light. Since red light penetrates much more deeply into animal tissues than does blue or ultraviolet radiation, larger animals would be more strongly affected by the beneficial fractions of sunlight – the internal tissues receive only red light.

The winter sickness and stress of darkness that I have talked about so much are metabolic disturbances resulting from inefficient respiration, and involve fatigue, hypoglycemia with sugar cravings, and hormone imbalances which lead to nutritional problems, such as vitamin A deficiency.

Although healthy respiration is many times more efficient than glycolysis in producing usable energy, the combined effects of getting adequate red light and using butter and coconut oil instead of unsaturated oils will cause a great increase in energy consumption. People with a significant amount of fat in their body, who have in the past eaten foods containing vegetable oils, are likely to draw unsaturated fats out of storage, with toxic effects unless vitamin E, thyroid, and coconut oil are used protectively until tissue stores of unsaturated fats are depleted. (Typically, body stores of fat take four years to completely reflect the change to a different type of dietary fat.)

Coconut oil is rich in lauric acid, which is being discussed lately as an anti-viral agent. Lauric acid inhibits glycolysis, so coconut oil will tend to prevent hypoglycemia, while providing non-glycolytic calories directly to the respiratory system.

Milk and shrimp can contribute to mitochondrial respiratory efficiency, since milk has a low iron content, and shrimp are very rich in copper. Iron is an important catalyst in the formation of free radicals, and copper is involved in protecting against iron, as well as in the function of cytochrome oxidase. (Even before Hartroft and Porta discussed, in 1967, the free-radical promoting activity of iron which forms "age-pigment," iron was known as a carcinogen or cancer promoter. (J. Balo and I. Banga, "Effect of metal complexes upon experimental carcinoma," *Acta Un. Int. Cancer*, 13, 463-5, 1957; A. Haddow and E.S. Horning, "On the carcinogenicity of an iron-dextran complex," *J. Nat. Cancer Inst.* 24, 109, 1960.)

Anemia can cause fatigue, and iron (like arsenic) tends to stimulate the formation of red blood cells, so many people advocate iron supplements for chronic fatigue. Although the immediate effect is to deliver more blood to the tissues, providing more energy, the long-range effects are not good, especially when iron is added to a diet containing significant amounts of the unsaturated fats. When anemia is caused by something other than iron deficiency (and it usually is), it is important to find the actual cause. Thyroid deficiency, estrogen excess, various vitamin deficiencies, protein deficiency, and various other mineral deficiencies should be considered.

Reference: *Journal of the National Cancer Institute* 24(109), 1960.

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Insomnia & Hyperactivity

by Ray Peat, Ph.D.
Ray Peat's Newsletter

Sometime after my teens, I became a light sleeper. I found that if I stayed up too late it was hard for me to go to sleep, and then when I slept it was restless and dream-disturbed sleep. I suspected that my hormonal state was in some way analogous to that of new mothers, who wake at the slightest sound from their infant. A friend of mine had an episode of psychosis after her child was born, and I began to think about the frequent association of post-partum hypothyroidism with emotional or perceptual problems. Although I tended to be hypermetabolic, and had been puzzled for years about the co-existence of signs of both hyper- and hypothyroidism, I finally tried taking thyroid. Immediately, I was able to sleep easily and deeply, and my need for food decreased. It was obvious that thyroid was having a quieting effect on my whole metabolism. I slept more efficiently, woke up refreshed, and had abundant energy during the daylight hours, and began looking for chores to do around the house, just for fun. Before taking thyroid, the first thing I did every morning was to drink two or three cups of coffee, but a few days after taking thyroid I noticed I didn't think about coffee very often, and I drank about 90% less, without feeling any withdrawal symptoms.

Since the 1960s, a stimulant, Ritalin (methylphenidate) has often been prescribed for hyperactive kids, because it made them able to quietly pay attention. This effect was called "paradoxical," but – for scientific physiology – there was nothing paradoxical about it. The frontal lobes of the brain, the most highly evolved part, give us the ability to plan and to understand complex things that require prolonged attention. Without this higher part of the brain which has a very high energy requirement, people and animals become hyperactive and unable to concentrate. Ritalin (or coffee) makes anyone, even the brightest students, more attentive and focussed. Caffeine and Ritalin temporarily raise the energy level of the brain. Thyroid hormones are essential for providing the energy to keep the brain at a high energy level all the time. If these hormones are deficient, our nerves need stimulants to function normally, and our bodies ordinarily produce large amounts of adrenalin to keep us going. The result is that we get tired and tense at the same time.

An old and useful test of thyroid function uses the Achilles tendon reflex, to observe the relaxation speed of the calf muscle. In hypothyroid states, the muscle is slow to relax, because the cells are slow to replace the energy used by the contraction-twitch. Because of the slow energy production, the muscles tend to fatigue easily, and to swell and feel sore with moderate exercise. In children, painful, swollen and tense muscles sometimes make it hard to go to sleep after an active day.

In the heart, slow replacement of energy can be seen in the EKG, as a delayed and depressed T wave; if this is combined with stress and excitement, it can cause a rhythm disturbance.

The brain is just like muscle, in having to restore its energy to relax. Many people have noticed that eating a lot of carbohydrate and/or salt makes them sleepy. Both salt and carbohydrate tend to lower adrenalin, and carbohydrate can also increase the activity of thyroid hormone, while restoring energy to the tissues.

In the last 20 years, I have seen almost everyone's insomnia disappear when they correct their hypothyroidism, sometimes just with dietary changes, but more often with a thyroid supplement. Many times, people have told me that they get to sleep within a few minutes when they take a minimal dose of thyroid at bedtime. By increasing the rate of energy production, relaxation and sleep are made possible.

In 1973 (in my book, *Mind and Tissue*) I reviewed old studies of cellular inhibition, which distinguished between the naturally quiet resting state of energized cells, and the state of protective inhibition, which prevents injury or death from overstimulation and fatigue. In our "establishment physiology," there has been no coherent theory of cellular inhibition, which means that cellular activity could hardly be understood correctly, either. Most of the facts are known, but they have seldom been put together in meaningful patterns, which would let us see that a few simple principles govern a great range of disturbing phenomena: seizures, shock, hypertension, fibrillation, cramps, restless legs, coma, insomnia, obsessive thinking, migraine, hyperactivity, even cell death and aging. ➤

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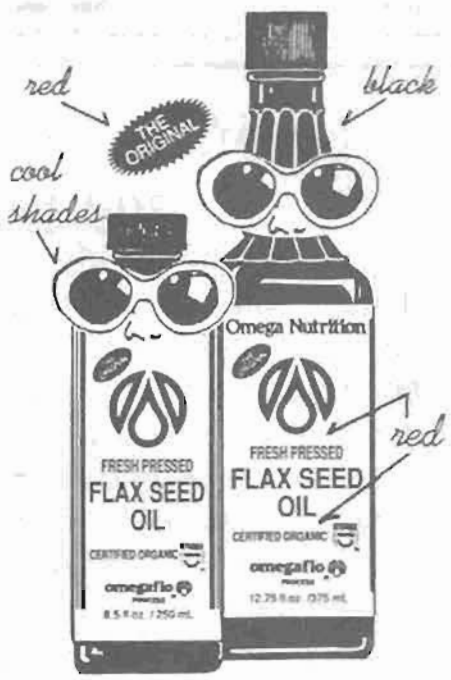

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Insomnia & Hyperactivity

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Coherent theories have been rejected because they don't suit the dogma of the establishment physiologists, who like to explain things in terms of hypothetical "membrane pumps." A few fetish ideas dominate physiology, just as the gene and virus fetishes have governed cancer research. For more than a century, most physiologists have "explained" muscle soreness as being "caused by lactic acid," while generally ignoring the great swelling of muscles that results from intense exercise. When cells don't have enough energy – whether from inadequate fuel, overwork, lack of oxygen, or poisoning – they take up water. Too much water tends to excite the cells, and can even stimulate cell division. The hyperactive state of a muscle cell, cramping, causes energy to be spent. What is too often overlooked is that the cell needs more energy to get back into its resting state, and that an abundance of glucose or other fuel, oxygen, and thyroid are needed for the cell to produce energy fast enough to become quietly relaxed. Albert Szent-Györgyi demonstrated that rigor mortis, the stiffening of the body that occurs after death, is just an energy deficiency, like a final cramp: he injected ATP (the tissue "energy molecule") into a stiff animal, and its tissues' softness was restored. The idea of "membrane pumps" keeps many people from seeing the implications of experiments like that. Intravenous injection of ATP cures shock, restoring normal circulation and tissue function, but again, the idea of membranes and their pumps has kept mainline science on its relatively sterile track.

The reluctance to see something as simple as the swelling of a muscle when its energy is depleted, has led into other unnecessary confusions. For example, the water that the muscle takes up comes from the blood. The blood gets thicker, and is harder to pump. The loss of water from the blood makes it seem that hormones have increased, when actually they may have decreased. If the tissues could be re-energized, they would release some of their water back to the blood.

For many years, a few physicians have known about the quieting effects of thyroid, and have prescribed it for hyperactive kids, as well as for lethargic ones, and for otherwise healthy kids with "growing pains." Since the mid-1950s, there has been a terrible increase in the incidence of hyperactivity in children, as discussed by Tom Brewer, largely because of prenatal injury. The increased use of unsaturated vegetable oils (proven to cause brain damage in rats) has certainly played a role. The more unsaturated an oil is, the more strongly it interferes with thyroid secretion, the transport of thyroid hormone in the blood, and the response of the tissue thyroid receptors. Hypothyroidism, both prenatally and during childhood, severely limits development of the brain.

It is a simple fact that nerve cells must have an abundance of energy if they are to be able to relax. Every physician knows about the convulsions produced by extreme hypoglycemia, and some know that a lack of oxygen can produce convulsion, but few realize that a high energy state is needed for stable nervous relaxation. Otherwise, no one would hesitate to use thyroid hormone (and its energy-associated co-factor, magnesium) for insomnia, hyperactivity, and the whole range of energy-related problems. (Incidentally, thyroxine alone can be counter-productive, by competing with the respiration-promoting triiodothyronine, and by suppressing TSH secretion even when T3 is deficient. Similarly, a normal or high level of thyroxine in the blood doesn't mean that the person isn't hypothyroid, since T3 is the active hormone. Most of our T3 is produced in the liver.)

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Reference

S.M. Talaat, et al., The effect of ATP administration in irreversible shock, *Physiologist* 6:284, Aug. 1963.

◆

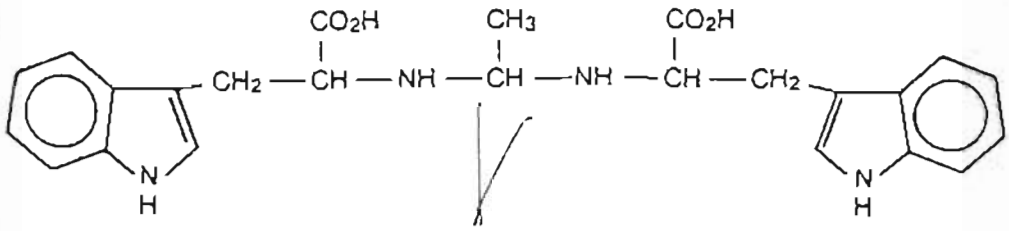
Quoting Thomas Jefferson 200 Years Ago

"If we run into such debts as that we must be taxed in our meat and in our drink, in our necessaries and our comforts, in our labors and our amusements, for our callings and our creeds, as the people of England are, our people, like them, must come to labor sixteen hours in the twenty-four, [and] give the earnings of fifteen of these to the government for their debts and daily expenses; and the sixteenth being insufficient to afford us bread, we must live, as they now do, on oatmeal and potatoes; have no time to think, no means of calling the mismanagers to account; but be glad to obtain subsistence by hiring ourselves to rivet their chains on the necks of our fellow sufferers.... And this is the tendency of all human governments. A departure from principle in one instance becomes a precedent for a second, that second for a third, and so on till the bulk of the society is reduced to be mere automatons of misery, to have no sensibilities left but for sinning and suffering.... And the fore horse of this frightful team is public debt. Taxation follows that, and in its train wretchedness and oppression."

More Letters

treatment regimen has been published in *Advances in Therapy*, [July/August 1990;7(4): 206-28].

5. Recently, the CDC (Center for Disease Control) has identified peak 97, (or peak E) as Di-L-tryptophan aminal of acetaldehyde (see below). Although peak E was associated with EMS, research continues to determine if this substance (represented by peak E) is the actual contaminant. [*MMWR*. August 1990;39(34):589-91]



Some Final Notes

- L-tryptophan has been used in research without serious side-effects for over 30 years.
- It is an established fact that there is no association between Tyson and Integrated Health products and the disorder EMS. Tyson and Associates has had its L-tryptophan analyzed by numerous laboratories and no contamination has been found in any Tyson or Integrated Health L-tryptophan product.
- HPLC (High Performance Liquid Chromatography) analysis of the Showa Denko finished product (tablets) and raw material are on file at Tyson and Associates, Inc. This analysis showed the same type of data that was published in the *New England Journal of Medicine*, [August 9, 1990;323, (6)], which demonstrated many unidentified peaks in addition to L-tryptophan .
- Again, we want to affirm that pure L-tryptophan is safe at the normal dosage of 500 mg to 3000 mg taken daily with the proper co-factors.

Thank you for your support in the past and we will continue to inform you of any new developments.

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Glycyrrhizin Supplementation Benefited by Methionine Administration

Editor:

I read with interest Paul Bergner's article on Japanese research on glycyrrhizin and the potential usefulness of licorice root (Glycyrrhiza glabra) for those with AIDS or ARC or who are HIV positive. As with its other applications, the utilization of licorice here is limited by glycyrrhizin's mineral corticoid activity which causes excretion of potassium and retention of sodium, thereby increasing fluid volume and blood pressure with long term use. I would like to bring to your readers' attention a Japanese study by T. Mori et al. published in *Oyo Yakure* 34:293-301 (1987) (English abstract found in *Chem. Abs.* 108:49307t) which tested both methionine and amino acetic acid alone and in combination in rats as a means of blocking these side effects of glycyrrhizin. They found that both substances individually or together, when given with glycyrrhizin, helped prevent the fluid retention by increasing sodium excretion and urine volume. Since DL-methionine has been used in a number of lipotropic formulations at approximately 1 gram/day for some time, this supplemental use is apparently safe. If its use with Glycyrrhiza is successful in preventing the development of hypokalemia and hypertension in humans, then the benefits from this plant can be extended beyond their current limits.

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Bowel Toxins Accelerate Aging Process

Editor:

The gerontologist, V.V. Frolkis, recently found that mice lived 43% longer than animals on the standard diet when they periodically had activated charcoal added to their food. This is the clearest evidence I have seen that "bowel toxins" make a major contribution to the aging process. Although I think carrot fiber would have a similar effect, there might be important differences in the substances bound by wet cellulose and by microporous carbon. Analysis of the substances bound to the charcoal after it has been excreted should give us important new knowledge about aging. Besides endotoxin, I think the charcoal might protect against microbial estrogen and glucocorticoids, carbon monoxide, cyanide, and unsaturated oils. Absorption of heavy metals is probably decreased by all types of "fiber."

While Bogomoletz and Metchnikof saw the bowel toxins as the factor which drove the aging process, I see bowel toxins rather as a relatively late-acting factor that accelerates a process which develops for other reasons. Once our detoxifying mechanisms begin to fail, bowel toxins pass the bowel with relative ease, and rapidly destroy the remaining systems of defense and detoxification. The altered hormonal environment and weakened digestion of an aging organism create a new balance between the animal and the bowel flora, sometimes allowing the proliferation of more toxic flora. The accumulation of iron and other heavy metals, and of unsaturated fats, and the progressive loss of copper under the influence of the stress of darkness, are probably the central events in the process of aging.

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of later stages of the disease) come into view, the **higher** potencies are required.

Generally speaking, diseases characterized by diminished vital action require **lower** potencies, while diseases characterized by increased vital action respond better to **higher** potencies, but this again is modified by the temperament and constitution of the patient.

If the grade of the disease is low and the power of reaction is low, the remedy must be given **low.** Incurable or terminal conditions, when the patient does not respond to well selected remedies, nor to intercurrent reaction remedies, given in potentized form and small doses, require us to resort to the **crude medicine** and increase the quantity of the dose up to the point of reaction: when reasonably sure of the remedy, give the **mother tincture** or a **low trituration,** first in moderate, then in increasing doses until the dosage is found to which the patient will react - the 'maximum dose' may sometimes be the *minimum dose necessary to bring about reaction.* This does not in the least degree violate the principle of the minimum dose *in such cases:* the principle of similars as applied in the selection of *both remedy and dose* is eternally and universally true. It is as true in terminal conditions in chronic diseases marked by gross pathological lesions, as it is in any other kind of case....

Thus the whole matter of the dose resolves itself into a problem of individualization. Looking at this subject broadly and having the highest degree of success in view, it is seen that it is as necessary to individualize the dose as it is the remedy, and ***that the whole scale of potencies must be open to the prescriber!***

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We must learn how to judge the degree of susceptibility if we would be successful homeopathic prescribers; and this applies not only to the normal susceptibility of the patient as evidenced by his constitution, temperament, etc. but to the varying degrees of his susceptibility as modified by the character and stages of his disease and by previous treatment. At one stage he may need a low potency, and at another stage, a high potency.

The man who confines himself to the use of a single potency, or two or three potencies, be they low or high, is not availing himself of all the measures of his art *and will frequently fail to cure.*

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Brain Aging

Editor:

Elie Mechnikov, like Pavlov, built a broad understanding of the nature of animals from a basic study of the process of nutrition. He believed that in the development of an individual, and in evolution, there is an early stage in which a division of labor occurs, with some cells being responsible for movement, and other cells (the amoeboid phagocytes) being responsible for ingesting and digesting food. The nutritional function of these latter cells was the basis for building and shaping tissues, and as the complexity of the organism increased, the phagocytes remained central in the preservation of the integrity of the organism.

Some examples will illustrate the ways in which phagocytic white blood cells preserve integrity. In a wound, white blood cells arrive quickly. Foreign matter, such as bacteria, is ingested and destroyed. If the object is too large to ingest, the cells adhere to it, and seal it off. Other white blood cells participate in healing, wound closing, and scar formation. Damaged or virus - infected cells of the organism, or cancer cells, or "old" red blood cells are destroyed and removed. Tissue remodeling - ranging from the tadpole's shrinking tail to the reshaping of bone by osteoclasts - is handled by this sort of cell. (That is, removal, replacement, and alteration of tissue are handled by this system.)

The energy available to the white cells, and the condition of the various tissue cells, govern the processes of phagocytosis, healing, and tissue remodeling. Thyroid hormone and body temperature are important factors governing the activity of white cells. The rate of movement of white cells through the tissue is strongly dependent upon temperature[1] (with the rate increasing with an increase in temperature), and they are generally tolerant of very high temperatures.[2] The conditions governing resorption of the tadpole's tail are probably relevant to how white blood cells function in mammals. Either cold or hypothyroidism tends to suppress or delay the phagocytic activity in the tadpole tail. With an adequate temperature and thyroid hormone, the cells selectively remove the oldest cells first, indicating that they recognize cellular age.

Although Mechnikov believed that the phagocytes were responsible for the atrophy of aging, he also believed that bacterial toxins from the intestine dominated the aging process.

Bacterial endotoxin inhibits mitochondrial respiration, and this respiration is needed for the intramitochondrial conversion of cholesterol into pregnenolone. With aging, pregnenolone and its derivatives, progesterone and DHEA, decline sharply. The brain, the organ with the highest concentration of those stabilizing substances, has many systems for adapting to their decreasing concentration, but the immune system is probably less able to compensate for those aging changes.

The combination of an extreme decrease in concentration of the protective steroids in the brain, and impaired function of the phagocytes, might account for some of the features of Alzheimer's disease. In this disease, microtubules accumulate within nerve cells and other nerve cells die, leaving tangles of their axons, including microtubules. These cells are not removed, as dead cells normally are. Subnormal temperature and hypothyroidism probably contribute to the inertia of the phagocytes. (In mammalian cells, microtubules dissolve at low temperatures, and are stable at higher

temperatures. Phagocytosis seems to depend on a functional microtubule system within the white cells.)

But the reason for the nerve cell's death, and for the tangles of filaments within living cells, seems to be a metabolic problem of the nerve cells themselves. A few years ago, there was talk of a similarity between the "amyloid" deposits, and the blood protein, pre-albumin. Since that protein transports vitamin A and thyroxin, I wondered about the possible effects of a vitamin A deficiency. Vitamin A regulates lysosomes, and so a deficiency might promote the accumulation of intracellular debris. It is an antioxidant, and so a deficiency might tend to induce the stress-hypoxia proteins, and it is used massively in the synthesis of steroids (for example, progesterone supplementation spares vitamin A). But possibly most important is the "de-differentiation" that occurs in many cells in a vitamin A deficiency. In the skin and mucous membranes, a vitamin A deficiency acts like an excess of estrogen, to promote the formation of keratin.

Twenty years ago, English researchers found virus-like shapes in the brains of old people, and suggested that senility might be caused by a virus. Later, one of them found that aged brain tissue was antigenically similar to scrapie-infected brain tissue from a young animal, and antigenically distinct from healthy young tissue.[3]

In size and over-all structure, keratin filaments are similar to the scrapie particles, and to the filaments that accumulate in Alzheimer's disease. I think of keratin as a protein made by a cell which has lost the energy to make more functional proteins. Normally, keratinized cells are formed by rapid cell division at a body surface, where little energy is available. In chronic vitamin A deficiency, the keratin-forming cells divide more rapdily than normal. Dandruff and the moist white equivalent of dandruff on mucous membranes, leucoplakia, are promoted by a deficiency of vitamin A, or an excess of estrogen. Radiation often causes a similar hyperkeratosis, probably by destroying vitamin A, and, like estrogen, by creating a respiratory effect. I suspect that the plaques in Alzheimer's disease are the brain's equivalent to the plaques of leucoplakia, or of dandruff, and that the overgrowth of the glial cells is the result of the same tendency of cells to divide rapidly, while the non-dividing neurons accumulate an excess of fibrous proteins that can't be degraded.

In degenerative diseases, the stress - and age - induced accumulation of iron and other mitochondria-toxic material (e.g., calcium, aluminum, and lipid peroxidation products including age-pigment) and the failure of detoxifying systems make therapy with ordinary nutritional supplements fairly ineffective. Direct supplementation of the various natural protective substances (or their analogues) in addition to the protective vitamins (especially E) and minerals (especially magnesium) is more appropriate.

The supplementation of prenenolone, etc., will allow dietary vitamin A to be spared for other purposes, including regulation of mitosis, differentation, and oxidation.

GABA-related metabolites, such as GHB, butyric acid, succinic acid, and the butyrobetaines, have multiple protective functions, including promotion of respiration and pregnenolone synthesis, regulating gene expression, and reducing damage from glucocorticoids.

DHEA seems to be involved in various regenerative processes, and a deficiency of it is prognostic of increased probability of death from various causes, including cancer, heart disease, and AIDS.

Progesterone has the special status of being an essential nerve growth factor, and generally blocks the catabolic actions of the glucocorticoids and estrogen, thereby protecting all tissues, from brain cells to white blood cells.

Thyroid hormone protects against stress and supports normal differentiation.

Short and medium-chain saturated fatty acids provide a safe source of energy, as well as having hormone-like and adaptogenic effects. The short-chain saturated fatty acids are important in regulating bowel flora. Mechnikov's idea of altering the flora with cultured milk was on the right track, but much more needs to be done on bacterial nutrition and toxin formation.

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More Letters

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Carbon Monoxide: Cancer Hormone?

When I started graduate school in biology at the University of Oregon, cell "membrane" research was a thriving business, almost as lucrative as genetics. Years earlier, I had been intrigued by Linus Pauling's suggestion that anesthetics might act by "structuring" the water in nerve cells, and in trying to understand the physiology of hearing, I had concluded that the "unit discharge" (all-or nothing) idea of nervous transmission left almost everything unexplained. As a result, I concentrated on the organized internal complexity of structure in cells, and found no reason to believe that cells were bags of randomly acting enzymes enclosed in an "amazing membrane" which contained an array of pumps that regulated the composition of the enclosed fluid. When people produced pictures of"membrane pores," I thought they should also have to explain why pores of the same size appear when distilled water is frozen and photographed by the same techniques. If a red blood cell, when etched awa y microscopically looks like a sponge, how can a hypothetical membrane on the surface be all-important? Why did it take so long for electron microscopists to produce images of the membrane, when their microscopes were producing fine images, and why did it take several decades for them to decide how thick these membranes should be? Reading the history of the theory of the "plasma membrane," I decided that it was almost perfectly irrelevant to biology, because dead cells, as in hair, can demonstrate the same ionic gradients that were the reason for believing in the regulatory membrane.

Many people think of the membrane inside an egg shell when they hear people talk about the "cell membrane," but the standard lipid bilayer membrane to which so much importance is given should evoke an image of the iridescent sheen that can be seen on puddles when a trace of oil spreads over the surface. This spreading of oil over a mass of water is precisely the physical model that lies behind the membrane theory. But the proteins making up the cell have a great affinity for fats - the cell is far from being the watery mass that the theory says needs to be separated from its environment by an oily film.

When electron microscopes became available, people expected to see the cell membranes they believed in. But in the first pictures, no membranes were visible. After many trials, methods were found to create the appearance of a membrane on cells, but for more than 20 years microscopists were arguing over the thickness of the membrane. The images showed membranes that were as thin as 20 Angstrom units, or as thick as 300 Angstroms. After 30 years, their thickness was decided to be between 60 and 100 Angstrom units. Osmium, which is the standard material used for producing images of cell membranes, was already in medical use for creating "false membranes" on burned or ulcerated tissue. How do you suppose this material came to be used to reveal the membranes which theory required, but ordinary techniques didn't show?

I believe fats are important in carcinogenesis, but not because of any theoretical membrane function. They have regulatory functions, and I think it is important to avoid associating the idea of "regulation" with the misleading idea of "membranes."

Around the same time, I read the history of genetic thinking, and found that Weissmanism, which formed the basic orientation for contemporary thinking in genetics, was ludicrously mistaken. The technical definition of the "gene" has quietly changed over the last couple of generations, but the term has kept its mystique, which leads people to

feel that they have explained something when they can identify "its gene." The mystique carries so much weight, that it is customary to accept conclusions regarding "genetic causation" without ordinary statistical support.

At the time I began studying biology at the University, the brain was explained in terms of genes and membranes, with emphasis on membranes, and cancer was explained by genes and membranes, and the dominant thought was that a genetic defect caused a membrane defect, which caused the abnormal behavior of cancer cells. To an outsider, the idea sounded as defective then as it does now, but rhetoric is very important in science, and it was rhetorically persuasive to most scientists.

I have been hearing people say "we don't know what causes cancer, but we are certain it's genetic." John Gofman, in his new book,(1) argues that 75% of breast cancer is caused by exposure to radiation, and expresses annoyance that so many people seem to forget that radiation is well established as an important cause of the disease. He quotes a statement from a fund-raising appeal: "What's worse, even the best doctors have no idea what causes breast cancer or how to cure it." (The 75% figure might sound high at first, until you realize that the incidence of breast cancer in the U.S. has doubled since 1970.)

Samuel Epstein says that the National Cancer Institute and American Cancer Society are indifferent to or ignorant of cancer prevention.(2) He cites exposure "to chemical and radioactive carcinogens (notably large scale emissions and discharges from civilian nuclear reactors)" as known causes of breast cancer, and mentions "the cancer establishment's exploitation of women as scientific guinea pigs as evidenced by: their deliberate exposure of some 300,000 women without warning to high dose mammography in the 1970s; their failure to recognize the carcinogenic hazards of current `low dose' mammography...." Epstein also mentions that "exogenous estrogens synergize the carcinogenic effects of irradiation..."

So, we could reverse the popular claim of the cancer establishment, and say that most of the causes of breast cancer are now known.

Since the 1950s, when Gofman worked for the government and was himself a "radiation apologist," I have followed his work, and have admired his ability to free himself from mistaken views, even when doing so was costly to his career. He now holds the establishment view regarding the nature of cancer: He says it "is now considered to be a genetic disease. It is thought that a tumor develops in stages from a single cell, as the cell and some of its descendants accumulate a set of several `genetic lesions.'"

I am strongly inclined to doubt this part of the establishment view, too. I have mentioned some of the evidence against it in a previous newsletter For many years, histologists studying carcinogenesis in animals have seen diffuse changes in cells throughout the area which has been irradiated or chemically treated, where the cancer will appear. The uniformity of the precancerous tissue shows either that the "genetic lesion" isn't random, or that it is already invasive, though not yet cancerous. If we want to emphasize the "genes," we will say that certain genes are very susceptible to mutations, and that, once a mass of precancerous mutated cells exist, it is likely that other mutations will occur in those cells, "promoting" them from a precancerous to a cancerous state. But the outstanding feature of genetic mutations, which geneticists have insisted upon, is that

they are different from physiological changes in being random. The very idea of "promotion," which is now an accept ed part of the doctrine, violates the traditional idea of what a mutation is. This issue has been coming up repeatedly in connection with the ideas of the cancer gene, the cancer virus, or the viral cancer gene: The gene (or virus) "is activated by the carcinogens or radiation," which amounts to saying that something - e.g., radiation or chemicals or hormones - causes cancer, leaving the cancer gene unable to explain anything.

In fact, the well-accepted tumor "promoters," estrogen(3) and unsaturated fatty acids, turn out experimentally to be fundamental carcinogens, as well as promoters. Phorbol esters, famous as experimental tumor promoters, activate a particular cellular system, which is also activated by unsaturated fatty acids, and by various hormones. Unsaturated fatty acids are now clearly identified as a "target" of ultraviolet radiation damage in skin cells, and increasingly they are seen to be involved in toxic injury and stress injury. Radiation absorbed anywhere in a cell can start a peroxidation chain reaction, causing widespread damage, which can include the inactivation of important enzymes, including those known as "membrane pumps. "(4) These same chain reactions might also cause breaks in the DNA chain, producing mutations, but that is a separate question. If the antioxidant defenses and the energy reserves of the cell are depleted, permanent damage is very likely. People who see the c ell as being "essentially its genes" have denied that low-level radiation causes cancer, because they think about direct interactions between rays and genes. Even though most of the evidence has been deliberately suppressed and "lost" by the U.S. government, it is now very clear that low doses of radiation are carcinogenic.

The reason people want to say that cancer is "genetic" is simply that cancer cells have a stable identity which is propagated as they multiply. They, unlike the cells they derive from, are immortal, in the sense that they go on dividing, and don't mature into anything. They are said to be "dedifferentiated" cells, that are more like the cells of an embryo than like the cells of the tissue where they grow.

If cancer cells could mature into cells like those they came from, they would just be like any cell in the tissue-repair process. The cells we know as cancer are somehow stabilized in a relatively undifferentiated state, they inherit that state from the cells that precede them. It is reasonable to consider that genes might have something to do with being stuck in a condition of undifferentiated growth.

But there are many situations in which established, undifferentiated cancer cells have differentiated in the laboratory, under special conditions. This proves that, in those cases, the cancer was not a genetically caused thing, since the conditions didn't undo any mutation. For example, leukemia cells have differentiated after they were treated with DMSO or dimethyl formamide, for cold storage. Melanoma cells have reverted to a more differentiated type under the influence of the ophylline and testosterone. In one very interesting experiment, cells from a malignant tumor were combined with the cells of an embryo, and the mixed cells grew into a mature animal which was a mosaic, showing inheritance from four parents - that is, the cancer cells were just as good as healthy embryonic cells, and just needed the right environment to mature.

So, to me it seems that the real question is, "what can cause the stabilization of cells in the undifferentiated state, yet allow for certain conditions occasionally to restore the mature state?"

Some of the earliest cancer research demonstrated that tumor cells can be transplanted successfully into certain hosts, and not into others. This led many people to think about the various factors that might make some individuals resistant to cancer, and others susceptible. The immune system and hormones were found to be complexly involved in susceptibility. It occurred to some people that the cancer itself might produce a special hormone, that affected the host organism in a way that tended to allow the tumor to keep growing.

When extracts of cancers were injected into healthy animals, some of them became sick, and were inclined to develop cancer. Several lines of investigation led to the belief that pyrroles and porphyrins, related to heme (the iron-binding pigment in hemoglobin and various oxidative enzymes), might be a "cancer hormone," but the idea lacked charm, and didn't catch on.

I made extracts from aged uterine tissue, thinking it might contain estrogen, and found that when I injected it into a hamster, it seemed to cause secretion of porphyrin from the animal's eye. This led me to get interested in the hormonal significance of the porphyrin pigment, and it was known to be related to estrogen excess and cancer susceptibility.(5, 6)

Two of cancer's most mysterious features are its respiratory defect, identified by Otto Warburg, in which it converts glucose to lactic acid even in the presence of oxygen, and its resistance to lipid peroxidation. Lipid peroxidation is intimately involved in the control of cell division and aging, and in susceptibility of cells to elimination by the immune system, so cancer's antioxidative capacity seems to be closely related to its "immortal" nature. Iron (either free or bound to heine) is known to catalyze lipid peroxidation, but its presence in cancer cells simply supports their growth, rather than causing peroxidation.

Warburg discovered that light desorbs carbon monoxide and cyanide from respiratory pigments. In trying to understand light's effects on respiration, it occurred to me that it might be desorbing those, or other toxins that bind to and inhibit the respiratory enzymes. Cancer cells lack the ability to detoxify cyanide, so it has seemed possible that cyanide might contribute to the respiratory defect of cancer; bowel bacteria can produce small amounts.

But carbon monoxide is always being produced in the body, by the enzyme heme oxygenase, which is involved in the breakdown of hemoglobin. Carbon monoxide, by binding to heme-iron, inhibits lipid peroxidation,(7) as well as inhibiting the respiratory pigments in the mitochondria.

Warburg observed that depriving growing cells of oxygen was sufficient to cause some of them to turn into cancer cells.

Anything which causes oxygen deprivation stimulates the formation of heme.(8)

If the breakdown of heme occurs in cancer cells, that is, if heme oxygenase can be demonstrated in them, then the conditions exist for a stable, heritable but non-genetic state which, as a result of the carbon monoxide which is produced in heme metabolism, combines a respiratory defect with resistance to lipid peroxidation. Heme oxygenase is induced by a variety of stresses, especially oxidative stress,(9, 10) and is known to exist in at least some cancers."(11) I think it will turn out to be a universal feature of cancer.

Heme could function as a systemic toxin, if produced in cancer cells in abundance, since it would be metabolized in the liver, with production there of abnormally large amounts of carbon monoxide. Liver abnormalities have long been recognized as an important feature of cancer.

And carbon monoxide, produced by a large tumor, would certainly be a systemic toxin. It could also account for the "regional cancerization" which has been reported to occur in the area immediately around a tumor, in which normal cells seem to be modified by the cancer as if by an inductive agent. These observations have always been discounted by the genetic dogmatists.

The relation between estrogen and porphyrin (which can be seen in some types of porphyria), and their association with cancer susceptibility, probably is a consequence of estrogen's interference with blood oxygenation, which would tend to cause exaggerated production of heine in various tissues. A sensitive instrument is now available, which can measure carbon monoxide in the breath; this could become an important diagnostic instrument.

Besides using light to desorb toxins from the heme group, there are probably various ways to directly inhibit the formation of heme. For example, ethyl alcohol inhibits heine formation(12) (the "hemeless" ring sideroblast is often considered to be a sign of alcoholism). Alcohol is superior in many ways to morphine for pain control in cancer patients, and if carbon monoxide produced by heme breakdown turns out to be a factor in cancer's persistence, alcohol might become an important factor in the prevention or treatment of cancer. It would be necessary to use a highly purified form of vodka, free of estrogen and other carcinogens. Except for bowel and liver cancer, the alcohol should be taken transdermally or intravenously. Anti-inflammatory and antihistamine agents, magnesium, progesterone, pregnenolone and other substances could be used to support oxidative metabolism.

The material used in heme synthesis is diverted from energy production. Useless heme production would contribute to cancer's energy-depleting effect on the organism.

Although carbon monoxide production by cancer cells will seem merely an incidental feature to the genetic dogmatists, I think it offers the opportunity for a unifying perspective on cancer, explaining both its systemic effects (immune suppression, wasting, and adrenal activation, for example) and its cellular features, including the respiratory defect, dedifferentiation, resistance to killing by lipid peroxidation, and - in some ways the most important feature - its stability, which has led so many people to call it a "genetic disease." Metabolic stress does cause chromosomal damage and mutations, but without the intrinsic resistance to lipid peroxidation, these defects would lead to the cells' death.

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Townsend Letter for Doctors & Patients.

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By Ray Peat

Darkness, Water, Osteoporosis

By Raymond Peat

(Ray Peat's Newsletter)

Around 1973, there was an interesting observation, in which eyes that had been burned by ultraviolet rays were treated with red or infrared light, and the pain was relieved. Since I had been interested in solvated electrons, I wondered if this medical observation might involve a mechanism similar to the "bleaching" of trapped electrons in crystals or glass which has been colored by exposure to x-rays or gamma rays. Szent-Gyorgyi used to demonstrate that structured materials, e.g., ice, can stabilize excited states of electrons. He was curious about the existence of pigments inside organism, and suggested that they related to matabolic electrons, since he assumed that external light didn't reach these tissues.

In December, I drove in sunny weather all the way to Houston, and thought about light. Having read that the leaves of deciduous trees go into a negative protein balance (work by K. Thimann, U.C. Santa Cruz), as they age in the short days of autumn, I realized that the mechanisms of aging that I have discussed in other newsletters could be general for all living things. Knowing that plants have "photo-respiration," that is, the respiratory production of usable energy during stimulation by light, I wondered if animals might have something similar, accounting for winter sickness, dark-stress, and aging itself.

Knowing that photosynthesis uses orange-red light (though other plant processes are stimulated by other colors), I wondered if that frequency also stimulated photo-respiration. Anyone who has held their hand over a bright light knows that red light does penetrate tissue. Pineal researchers planted a photoelectric cell in a sheep's brain, near the pineal gland, to see whether significant amounts of light reached that organ directly, and the device clearly indicated when the animal moved from shade to sunlight. So, when I got home I was thinking about how to design an experiment to test the direct effect of red light on tissue respiration, especially in the brain.

I had been home for a couple of days, when a journal arrived in the mail, describing exactly the sort of experiment I needed to test the idea. Rats had a bright red laser beam shined on their heads for 15 minutes, and then the respiratory enzymes of the Krebs cycle was studied. The changes were consistent with enhanced respiration. (A. T. Pikulev, et al., Radiobiology 24(1):29-34, 1984.) (The red laser has been used for more than ten years to promote healing -- references will be provided on request.)

So my present thought is that darkness does in some way "poison" respiration, and that light enhances it, possibly by the indirect mechanism of disposing of electrons that have leaked out of the usable-energy pathway.

WHEN RESPIRATION IS blocked, tissue takes up water. A simple illustration of this is the cornea -- when contact lenses were very impermeable to oxygen, they caused severe corneal swelling. I think estrogen works by the same mechanism (and this explains why so many toxic substances are "estrogenic"). There was a doctrine that cells can move water only by moving sodium, so medical textbooks say that estrogen causes sodium retention; but it occurred to someone to actually measure the effects of estrogen on sodium and water, and they found that estrogen causes the fluids to become hypotonic, with a lower than normal sodium concentration.

Estrogen (like darkness and stress) promotes prolactin secretion. A previous newsletter discussed the experiments in which sodium suppressed prolactin secretion, while taking water without sodium stimulated it. So it seems likely that hypotonic (or sodium deficient) tissue fluids might be a common factor in the various situations which increase prolactin secretion.

In the salmon which swim up the Columbia river to spawn, the fresh water, which is very sodium deficient compared to the ocean, does stimulate the secretion of prolactin, and the prolactin is involved in their adaptation to the fresh water. The adaptation is very costly, though, because these fish undergo very rapid aging. Their bones are transformed in ways very similar to the bones of other animals in extreme old age: for example, the back humps and the jaw juts forward. (Since the fish vertebrae don't bear weight as those of a biped do, we shouldn't attribute the bending of the human spine in old age to "compression.")

Some recent studies have investigated prolactin's involvement in calcium disposition, and its contribution of osteoporosis. (J. A. Schlechte, et al., *J. Clin. Endocrinol. Metab.* 56:1120-1123, 1983; growth hormone is closely associated with prolactin, and I mentioned in Nutrition for Women that there was some basis for thinking that estrogen might make osteoporosis worse, acting through the growth hormone. The editor of the *Yearbook of Endocrinology* (1984, 273) says "Consider, if hyperprolactinemia leads to osteoporosis, and the administration of estrogens to postmenopausal women leads to hyperprolactinemia...")

Since it is established that excess prolactin does contribute to osteoporosis in humans, it seems reasonable to suppose that the dramatic increase in prolactin secretion when these animals enter fresh water would be the cause for the equally dramatic skeletal changes in the fish.

It is already known that excess calcium damages respiration and that calcium is associated with structural disruption of the mitochondria, and that tissues tend to calcify in aging. Inside cells, calcification begins in the mitochondria; outside cells, for example in blood vessel walls, the "ground substance" (a fine-textured component of connective tissue) can become calcified.

I think rational therapy for osteoporosis would include thyroid, Vitamin A, bright light, and either pregnenolone or a mixture of progesterone and DHEA, with a diet rich in protein and all the salts: calcium, magnesium, sodium, and potassium.

Hypotonic fluids are disruptive to life processes and structures. Even tissues which are not very cellular, such as cornea, joint cartilage, and the various "basement membranes" (which are rich in ground substance) can be damaged.

I suspect that we -- fish and humans -- have a simple way to protect ourselves from "hypotonicity," that is, from a deficiency of salts in our fluids. (There have been various observations in which one salt can substitute for another, at least to the extent of preventing an immediate disaster.) We carry with us a huge reservoir of minerals, our skeleton. In osmotic stress, it is better to lose bone material (and teeth) than to experience hypotonic disruption.

Undoubtedly the liberated calcium participates in adaptation in ways besides preventing swelling of the connective tissues, but I plan to examine the metabolic effects of calcium in future newsletters. (The bones also provide a large reservoir of sodium.)

Both prolactin and cortisone are secreted during stress (and in darkness), and both mobilize calcium. If calcium is so harmful to our energy producing system, why do the stress hormones dose us with it? I think this is largely explained by the generality of hypotonicity in stress, and by the convenience of the skeleton as a mineral reservoir. Selye illuminated estrogen by comparing it with the initial shock phase of the stress reaction (before adaptation begins), but the value of the comparison probably goes the other way, too: the essential element in stress is the inadequacy of energy to meet a challenge, and when energy is insufficient, water is taken up. (And some water is produced in the cell when oxygen is electronically reduced; this "respiration" is not necessarily in

Darkness, Water & Osteoporosis

Continued from page 130

volved in energy production — even "age pigment" can convert oxygen into water.)

Selye found that various stresses caused connective tissue disease, such as scleroderma and arthritis. He didn't explain the mechanism. I think it is significant that women are much more susceptible to many connective tissue diseases than are men. For example, a recent Arthritis Foundation advertisement says that women are twice as likely as men to suffer from arthritis. Fibrositis, myositis, etc., are common in women. (I think the studies of adhesions being prevented by progesterone provide a good model for understanding connective tissue disease, and allergies or "auto-immune" diseases; see Maurer and Bonaventura, *Fertility and Sterility 39* (4), p. 485, April 1983.) When cartilage is soaked in distilled water (or hypotonic body fluids) it swells with tremendous pressure. The microscopic mesh of this connective tissue is rich in negatively ionized groups, which attract neutralizing positive ions, such as potassium and sodium. As the neutralizing ions are leached away, the negative ions repel each other, causing swelling and attracting more water. As positively charged calcium ions are made available from the bones, the swelling is blocked. Continued for a long time, this seems likely to lead to conditions such as arteriosclerosis and scleroderma.

STRUCTURAL DISRUPTION of the mitochondria, as well as uncoupling phosphorylation from respiration, can be caused by cortisone. So it is interesting to see seasonal changes in the structure of the mitochondria, which are consistent with the ideas I have been talking about, that winter (and light deficiency in general) is what ages and kills us.

Winter stress, elevating cortisone, could also be the reason for the non-adaptive depression of thyroid function in the winter. Many people have noticed an association between stress and periodontal disease. Gum disease is common in hypothyroidism, and bone loss is an important part of the periodontal disease. This same endocrine pattern, and not "postmenopausal estrogen deficiency," is the most likely explanation for osteoporosis in aging women.

When I was working on my hamster thesis, about 1971, I noticed an article which reported that aging women's urine revealed an increased ration of estrogen to the 17-keto steroids. I think it was that article that started me thinking of aging generally in terms of a deficiency of anti-estrogens, including things such as DHEA.

DHEA has been studied in relation to osteoporosis. I. Hollo, et al., in *Acta. Med. Acad. Sci. Hung.* (Hungary) 35(1):53-59, 1978, reported that "Administration of norandrosterone decanoate or dehydroepiandrosterone to patients with menopausal osteoporosis resulted in normalization of the postload hypercalcemia. Calcium tolerance of menopausal patients without osteoporosis was not affected by dehydroepiandrosterone."

S. Brody, et al., in *Maturitas* (Netherlands) 4(2):113-122, 1982, found significant positive correlations "between basal levels of DHAS and the DHA response to ACTH respectively, and trabecular bone mineral content of the distal forearm."

There was a study of prolonged DHEA treatment on rat bones, which I haven't found: M. Boross, et al., *Aktuel. Gerontal* (Germany) 13(1):15-18, 1983.

I think rational therapy for osteoporosis would include thyroid, vitamin A, bright light, and either pregnenolone or a mixture of progesterone and DHEA, with a diet rich in protein and all the salts: calcium, magnesium, sodium, and potassium. A bias toward magnesium, rather than calcium, would protect against many conditions that occur in aging and stress.

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NOTE: A couple of other things to notice in regard to stress and season: in men, the sperm count, and in both sexes, the visibility of veins on the backs of hands when they are held at waist level.

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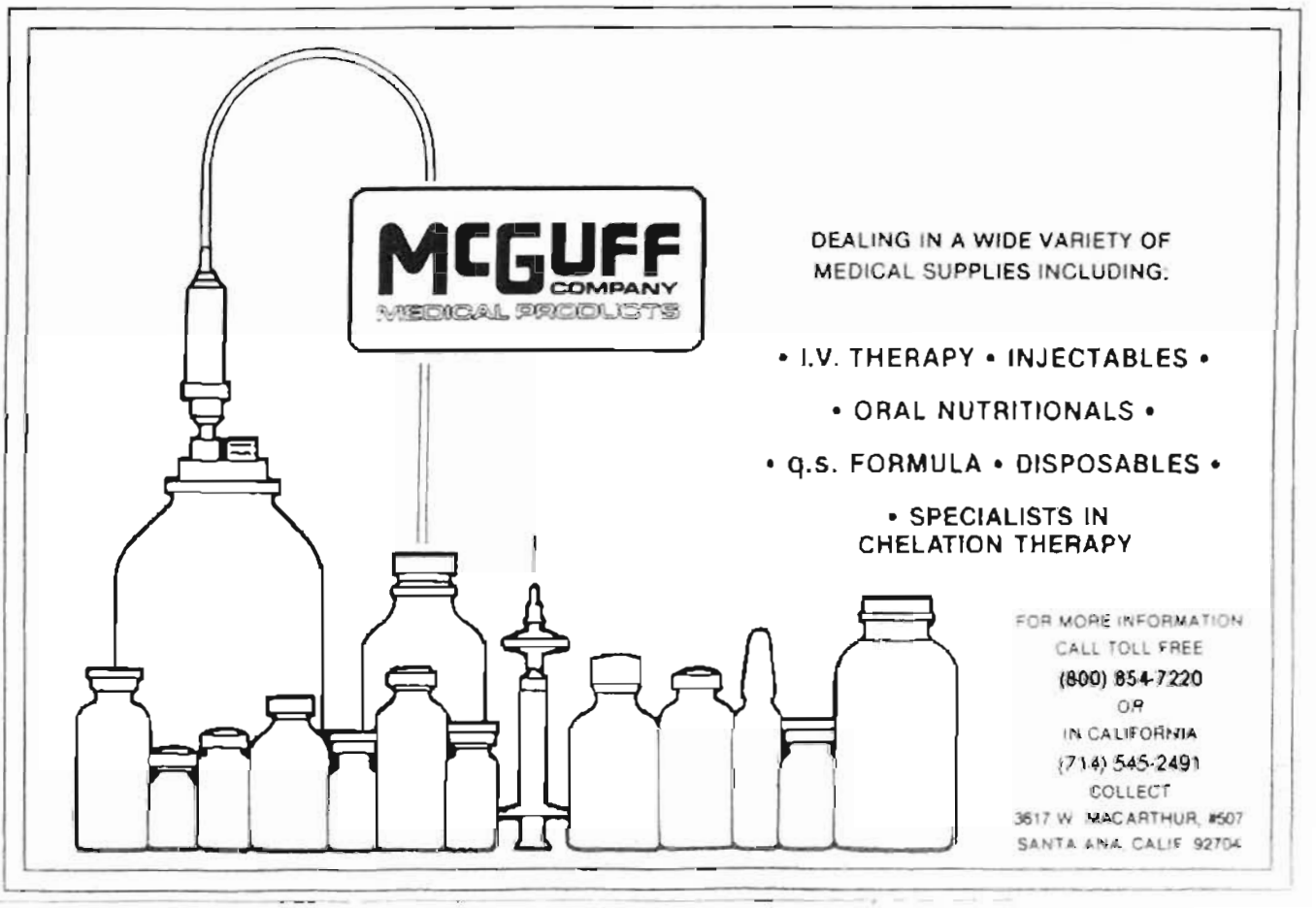

Medical Hypotheses

Aspects of Wholeness

by Ray Peat
Eugene, Oregon

"That a meeting-point between Biology and Physical Science may at some time be found, there is no reason for doubting. But we may confidently predict that if that meeting-point is found, and one of the two sciences is swallowed up, that one will not be Biology."

J.B.S. Haldane

Holism is the observation that, although natural objects can be resolved into their parts, the parts are to some extent shaped by their participation in the whole object. For example, in organic chemistry it is recognized that the reactivity of an atom or radical is modified by adjoining parts of the molecule, by the solvent, etc. Holism would never have been named, except that it is so common in our scientific tradition for someone to say "We know all there is to know about the parts (atoms, surfaces, fields, genes, etc.), so we can foresee the result of their combination." Good engineering involves knowing the properties of the materials so thoroughly that accurate predictions can be made about their behavior in new structures, but good science requires a willingness to accept the unpredicted when it occurs. Holism, or a non-dogmatic attitude toward the world, recognizes individual uniqueness, rather than averages, and is likely to look for complex causes (especially environmental influences), rather than too easily ascribing traits "to the genes."

Historically, a reluctance to distinguish our present knowledge from possible knowledge, and to distinguish our definition of something from its real existence and fullest potential, has characterized most of the people who oppose holism, and call themselves reductionists. Consciousness, perception, sensation, pleasure, and intention have often been omitted from the world described by reductionists. If we are going to understand life and its possibilities, then it seems that we should begin with an appreciation of its "liveliest" aspects, as an essential dimension of our thinking, even if we are going to work with some of its relatively inert aspects, such as viral genetics.

The relation of energy to structure is, I think, the central question of biology. (The importance of the same question for the physical sciences might indicate in a rough way how Haldane's predicted "swallowing up" might occur.) The ideas of resonance and hysteresis, which are only vaguely defined in physics, have to do with the interaction of energy and structure on various levels of complexity and organization, and are examples of physical concepts that can gain meaning and clarity from biology. When energy flows through matter, order accumulates (as a result of resonance and hysteresis, for example), but we hear so much about "entropy," "randomness," and "symmetry" that we forget most of the formative processes in the material world.

Human (and ecological) health obviously should have the benefits of holistic science, but the actual situation is that biology and medicine have become very product-oriented, and holistic considerations are increasingly left to a variety of "fringe" occupations. Many of these alternative approaches are concerned with the idea of "energy" as the key to health, but in general they lack simple and effective methods for optimizing biological energy, and often use counter-productive methods. In the following pages I will show how some of the most important achievements of ordinary science can be retrieved from the distortions of the medical promoters, and made available for holistic use, that is, for appropriate use.

Non-Genetic Biology

The word, "gene," itself contains an ideology, since it implies origin, or genesis, though its main meaning is something like "a unit of continuity." Building on the word's connotation, dogmatic geneticists explicitly stated their "central dogma": that information flows only from DNA to RNA, and only from RNA to protein. When Temin and Baltimore described the "reverse transcription" of DNA from RNA, all of the professional biologists I talked to said flatly that they didn't believe it was possible. Even when no one was threatening the addition of "information" to the chromosomes, the dominant belief among biologists was that development was closely controlled "by the genes," because the body owes its genesis to the genes. Intelligence, body proportions, and senescence were said to be "specified" or "governed" or "programmed" by the genes. The "congenital" condition was often taken as the "genetic" condition. Textbooks said that the maternal influence was only "genetic,"

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because the fetus was "insulated" from events in the mother's body (just as the "germ line" was isolated from events in the rest of the body). Although many kinds of experiments showed both prenatal and transgenerational influences of the environment on intelligence, body proportions, and rate of aging, the genetics-reductionist school ignored them, and defined themselves as the only scientific school of biology.

Mechanisms of Aging

Professor Soderwall and his students at the University of Oregon had shown that the corpora lutea (areas in the ovary which mainly produce progesterone) appeared to fail in aging hamsters, and that vitamin E supplements could extend fertility by a significant amount. His group showed that "aged ova" were not responsible for infertility, but rather that the uterine environment was not suitable for implantation. Soderwall had also demonstrated that excess estrogen could cause failure of the pregnancy at any point, from failure of the embryo to implant, to resorption of the fetus at a late stage of pregnancy.

Although I had investigated the association of estrogen with cancer, and knew from my own experience with migraines that stress, diet and hormones interacted in powerful ways, when I began to investigate the oxidative metabolism of the uterus I didn't realize that it would involve a convergence of several of my main interests. I was familiar with Otto Warburg's famous idea that cancer is caused by a "respiratory defect," and I knew that aged tissue had a diminished respiratory capacity. The textbooks indicated that estrogen deficiency and "aged ova" were responsible for senescent infertility. I found that the uterine endometrium of old animals often consumed oxygen at a high rate, and showed other signs of being under the influence of excessive estrogen. As I tried to understand this, I saw that several things could contribute to a high rate of oxygen consumption. Either too much estrogen, or too little progesterone could have the same effect, since it is the ratio between these hormones which controls their effects. A vitamin E deficiency increases oxygen consumption, and too much unsaturated fat has the same effect. In a vitamin E deficiency, unsaturated oils are oxidized in a way that produces "age pigment," also called ceroid pigment or lipofuscin. This pigment consumes both oxygen and fuel, but produces no usable energy. Estrogen excess synergizes with a deficiency of vitamin E to intensify the formation of this pigment. Partly, this might be because estrogen is a powerful stimulant of iron absorption, and iron is involved in the peroxidation that produces the pigment. But low oxygen concentration is what causes the iron to become active in peroxidation, and estrogen acts in several ways to decrease the availability of oxygen.

The way in which estrogen prevents or terminates pregnancy seems to be by causing the uterus to consume oxygen at such a high rate that there is no oxygen available for the embryo, which has a high requirement for oxygen beginning on the day that it normally implants. The chronic or cumulative effects of estrogen, leading to formation of lipofuscin, happen to act in the same direction as estrogen itself, causing oxygen to be reduced, especially in the uterus, but in all other tissues, too. Estrogen excess can also destroy the corpora lutea, interfering with the production of progesterone. Progesterone's effect in pregnancy is to assure the availability of oxygen and nutrients for the embryo, but it also has the general effect of inhibiting the formation of lipofuscin, and of other aging signs, by improving metabolic efficiency. (Progesterone is unusual among the anti-stress steroids in having no harmful side-effects.)

Although my work confirmed the other research that had been done in Soderwall's lab in the preceding 25 years, the idea that estrogen's influence appears to increase with aging, and even to contribute to the process of aging, was contrary to the doctrine that has been promoted by the pharmaceutical industry. Nevertheless, as I read more, I saw that there was really no evidence contrary to what I had seen in my own work. What existed was a web of interpretation which existed to sell estrogen treatments. Even the fact that estrogen causes abortion was "ignored," very consciously, until the industry had fabricated a more acceptable rationale with which to sell its "contraceptive" pills.

The idea of many factors acting in the same direction, and tending to have a cumulative effect, seemed to me to have a general biological significance. It seemed to be part of the answer to the question of what it is which is lost, or accumulated, during aging, which accounts for the decreased ability to adapt to the changing environment. It seemed to say something about the nature of Warburg's "respiratory defect" in cancer. The thyroid hormone, which governs respiration, is suppressed by estrogen, and by unsaturated fats. The wasteful metabolism of estrogen ➤

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dominance tends to use up glucose, and is likely to activate the stress hormones, including cortisol. The main features of aging can be produced directly by administering excessive amounts of cortisol. These features include atrophy of skin, arteries, muscle, bone, immune system, and parts of the brain, loss of pigment (melanin), deposition of fat in certain areas, and slowed conduction velocity of nerves. The physiology of aging (especially reproductive aging) overlaps the physiology of stress.

Puberty and Aging

Many studies have demonstrated that puberty seems to trigger the mechanism of aging, and the idea of a "death hormone," located in the pituitary gland, has been suggested. Many degenerative diseases develop under the influence of excessive estrogen and cortisone (and as a result of the many metabolic changes which follow exposure to those hormones). Many of these diseases, especially those which appear after puberty and are more frequent in women, can be treated very effectively with the anti-estrogen and anti-stress hormones, such as progesterone.

Hans Selye pointed out that estrogen treatment mimics the first, "shock" phase of the stress reaction. An excess of estrogen (or any stressor) causes the pituitary to secrete prolactin and ACTH, and both of these hormones act on the ovaries to stop progesterone production, and contribute in many other ways to the process of atrophy. ACTH, of course, stimulates the secretion of cortisol. The removal of the pituitary obviously isn't a practical way to delay senescence, but protection against the "death hormones" can be achieved to some extent by altering the diet to minimize the effects of estrogen and cortisol. Historical and demographic studies show that certain conditions affect the age at which puberty occurs. Ashley Montague has argued that we need more neoteny, that is, that we should try to preserve and to extend our youthful functions, because those are our most human qualities. If we can generalize from animal studies, delaying puberty could increase brain size and longevity, improve intelligence, decrease violence, and even make people physically more attractive (the "cute puppy" appearance is largely a matter of brain size in relation to the size of the face and body). I think this will be the next step in human evolution. Just as nurturing, stimulation, and freedom promote improvement in the function and structure of the brain, cruelty and oppression act in the opposite direction. If puberty is delayed, then the importance of a culture which supports curiosity, exploration, play and sensuous pleasure seems obvious.

The physiological age of the parts of an organism depends in some way on the developmental stage of the whole organism. This contradicts the reductionists' idea that cells or tissues have an "intrinsic" lifespan which will cause them to deteriorate after a certain limited number of divisions. When pieces of breast tissue or skin were repeatedly transplanted from old animals to young animals of the same (syngeneic) strain, they were still in good condition after ten "life-times," and their survival was apparently limited only by the necessity of trimming them each time they were transferred, to make sure that no host tissue was transplanted with them. When old rats were grafted onto young rats, the old member of the pair lived to twice the expected age. Recently, young female mice were grafted onto old females, to investigate any hormonal factors in aging. The ovaries of the young animal appeared to age, and its production of progesterone decreased.

This kind of evidence (and the simple observation that the cells in skin and intestine undergo thousands of divisions in an individual's life-time) strongly favors the idea that a systemic energy problem is involved in aging.

Energy and Evolution

When mammals and birds achieved the ability to sustain a high metabolic rate by keeping their bodies at a steady, fairly high, temperature, their "food chain," based on photosynthesis, consisted of organisms that generally lived at a lower temperature.

Sugars, proteins, and the saturated fats produced by warm organisms can be eaten by warm-blooded animals with no particular side-effects. Organisms that live at low temperatures, however, contain unsaturated fats. The consumption of large amounts of unsaturated fats lowers the metabolic rate, and accumulated unsaturated fats are susceptible to a spontaneous and toxic form of oxidation. (The toxic effects include damage to the respiratory apparatus and to the circulatory and immune systems, increased rate of aging, and cancer.) These "low energy" foods in effect counteract the evolutionary achievement of a high metabolic rate. Several studies show that decreased consumption of unsaturated fats can delay puberty. Other studies show that an excess of unsaturated oil in the mother's diet can damage the development of the fetus's brain. The choice of foods which have less unsaturated fat tends to reinforce the achievements of evolution.

The seed oil industry has created a national phobia about the consumption of saturated fats and cholesterol, but there is no basis for the idea that those foods should be avoided. People with hypothyroidism are susceptible to heart disease, but their elevated blood cholesterol becomes normal when their thyroid function is restored.

The body's highest concentration of cholesterol exists in the brain. The level of cholesterol in the blood strongly influences the production of the protective hormones, such as progesterone. The brain contains

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by far the body's highest concentration of these hormones.

In the winter and at night the respiratory energy producing system is damaged, and the protective hormones decline, and the harmful stress hormones increase. The immune system becomes less active, and mortality increases. Although ultraviolet light interacts with unsaturated fats in the skin to accelerate aging (E.R. Pinckney, *Medical Counterpoint,* Feb., 1973) and to produce cancer, ordinary visible light has several beneficial effects in animals. One effect is the "regeneration" of the enzyme SOD (superoxide dismutase), by causing its copper atom to be re-attached to the protein. Light also increases the activity of normal respiratory enzymes, and tends to normalize (or maximize) the production of hormones, including progesterone and thyroid. Animal migration to reproduce in regions with longer days is a way to benefit from this energy-promoting action of light. In adult birds, the increase of hormones in the spring causes the growth of new brain cells in the area that controls their singing. (In humans, the space inside the cranium keeps increasing into old age, and the amount of DNA in the brain also keeps increasing with age, but it has been assumed that such changes in adult brains result from an increase in the size of nerve cells, and an increase in the number of connective tissue cells, rather than from a continuing increase in the number of nerve cells.) I would expect an increase in the temperature of the earth, and increased use of artificial light (or migration) to lead to a prolongation of youth and the development of better brains.

Pollution

Besides the distortion of our food supply by the propaganda of the seed oil industry, there is increasing contamination of our food supply by heavy metals. Lead, for instance, has been spread everywhere, largely as a result of its use in leaded gasoline. Food additives are often contaminated with heavy metals from the sulfuric acid used in their manufacture. Practically everyone knows about the famous experiments in which food restriction increases the longevity of animals, as if eating were toxic. But removing toxic heavy metals from the food, without restricting the amount of food eaten, has had the same life-extending effect in experimental animals.

When estrogen is elevated (as at puberty, or in pregnancy, or with medical estrogen treatment) the absorption of iron is stimulated. During aging, the body's load of iron increases, especially if there is a deficiency of copper, and the body's content of copper decreases with age. Copper is an essential component of cytochrome oxidase, which has the crucial last position in the mitochondrial respiratory system. Copper is a component of the cytoplasmic SOD enzyme, which decreases with age. Ceruloplasmin, a major copper-containing protein, helps to keep iron in its safe oxidized form. Copper is involved in the production of melanin (itself an antioxidant) and elastin. The loss of melanin, elastin, and respiratory capacity, which is so characteristic of senescence, is also produced by excessive exposure to cortisol.

The protein, metallothionein, is rich in sulfhydryl groups, which bind heavy metals. It is assumed that this protein helps to detoxify and eliminate the toxic metals. This protein is induced by exposure to either a heavy metal or cortisol. A larger amount is produced in response to the combination of heavy metals and cortisol, than by either alone. Since copper, like the toxic metals cadmium, lead, mercury, and silver, reacts strongly with sulfhydryl groups, the body is likely to lose some copper when it is subjected to heavy metals or cortisol. I think this chronic loss of copper accounts for the obvious features of aging, such as loss of elasticity of the skin, lungs, and blood vessels, the depigmentation (demelanization) of skin, hair, and (in Parkinson's disease) substantia nigra, and for the decrease in respiratory capacity. The replacement of the copper by iron (and the loss of the copper-enzymes which protect against iron-catalyzed free radicals) probably accounts for the increased formation of lipofuscin during aging. When copper-dependent mitochondrial respiration fails, lipofuscin has the ability to sustain energy production through glycolysis (by keeping the coenzyme NAD, nicotinamide adenine dinucleotide, relatively oxidized), so it is possible that lipofuscin is a primitive sort of defense against stress.

In animals, copper supplementation can restore natural color to white hair, and in one experiment, it increased longevity. At present, there isn't enough knowledge about the safety of different ways of administering supplemental copper. It can be toxic, and it oxidizes other nutrients. Besides choosing foods high in copper and ➤

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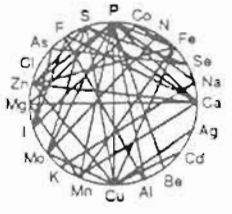

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low in iron and other heavy metals, other dietary choices which support thyroid function will tend to promote the retention of copper. Other dietary practices can minimize our production of cortisol (e.g., combining fruits and protein, since protein foods lower blood sugar and stimulate the secretion of cortisol).

Self-Regulation

Physical science provides a much richer picture of the qualities and potential of the material world than geneticists recognize. Even many physicists don't recognize the richness implied by the body of experimental results in their field. Many well-known physical scientists have had relatively holistic attitudes (e.g., J.C. Bose, Michael Polanyi, B.V. Deryagin, Frederick Soddy, V.I. Vernadsky). A rich view of physics has much to offer to biology. However, when I say that a holistic view of biology is open to using physics and chemistry, as well as ecology, history, and cosmology, to achieve an adequate understanding, I should mention that there is a school of weird (immaterial and "quantum" centered) physics which is presenting itself as a holistic world-view. To them, I think Einstein's remark still applies: "You believe in a dice-playing God and I in perfect laws in the world of things existing as real objects...." Elsewhere, Einstein observed that an object's fields amounted to an extension of its material substance, i.e., he preferred to materialize fields, rather than to dematerialize things, as some of the popular philosophers of physics do.

The orderly, epitaxial growth of crystals has been shown to occur across the thickness of a plastic film. A detailed study of this sort of long-range ordering process was made by Alexander Rothen. He was able to demonstrate biologically specific adsorption at relatively great distances. Many other types of research in adsorption fields and long-range order make it clear that the interactions of atoms and molecules in cells needn't be governed by either direct contact or by random motion. When cell components are rearranged, they return to their normal position in relation to other components, revealing a great capacity for self-assembly or self-ordering.

The medical tradition of naturopathy recognizes a great capacity of the body for self-regulation and self-healing. I think these attitudes can be usefully expanded now, in the light of new knowledge about energy and structure. On the short time scale in which we think about the health of an individual, and on the transgenerational scale relating to having healthier, more intelligent children, and on the evolutionary time scale, I think we can see a tendency, not just to preserve homeostasis, but to move upward in energy and greater generality of structure and function. To provide more energy and scope for using it stimulates our ability to use energy meaningfully.

Some Implications

There is considerable flexibility in living organisms, and in higher and lower levels of organization, and we can see some of the ways in which structures of different complexity accommodate themselves to the surrounding conditions of energy and structure.

The conditions under which the brain develops, including gestational support and the later nutritional-hormonal-behavioral conditions, the degree of stress and stimulation, contribute to the brain's

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structural complexity and metabolic energy use, and to the organism's ability to cope successfully with the environment.

Vicious circles of physiology often stabilize an organism on a low energy level, which may involve disease or rapid aging.

The existence of a few systems of positive feedback (self stimulation), however, indicates that in our fundamental structure we are biased in an expansive, upward direction. Progesterone (and its precursors, pregnenolone and cholesterol) and thyroid hormones participate in some of the important positive feedback systems, involving energy production, stress resistance, and brain growth.

In therapy and in everyday living we can try to protect and promote our energy-producing and energy-using systems by seeking the stimulation, the conditions of light and temperature, and the foods that are appropriate for our evolutionary level.

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in overall health, among the industrialized nations, according to the U.N. World Health organization. On page 4 of his 1988 report, the Surgeon General says it clearly: "Together, these diet-related conditions inflict a substantial burden of illness on Americans." It is felt by many holistic physicians that following basic RD advice, as taught in schools, has been and is "feeding" patients right into the medical disease pipeline. Delaying medical treatment, which RDs claim happens by the seeking of alternative advice, is convoluted logic since their advice may be a significant part of the cause of the medical problems in the first place. Sort of like the dentists who regularly gave their young patients candy after each treatment. Yet, the Colorado Dietetic Association claims that the public is endangered by nutritionists not certified as registered dietitians.

A realistic way to judge what potential harm natural nutritionists are causing the public is to check with the courts. We live in the most litigious country on earth, with by far more lawyers per capita than any other nation. Recently a video rental store in California was sued by an irate customer who got home and discovered the wrong movie in the case. Americans are off to the races when it comes to liability, and everything seems fair game, no matter how ridiculous. The number of court cases filed against nutritional practitioners is so small that it is hard to find data on it. Most of the extremely rare cases filed are actually filed by local medical societies and the state attorney generals for the practice of medicine without a license, not initially by a consumer who felt abused or victimized. State medical societies have actually sent "stooges" posing as patients to holistic medical offices and other natural health professionals to entrap them into the "practice of medicine" with nutrition. It has been that difficult to find injured nutritional health consumers. On the other hand, medical malpractice suits are so common that six-figure malpractice insurance premiums are not uncommon. Statistics show that most medical doctors will, at some time, be sued for malpractice. The question therefore is: *If harm is being done, where are all the victims and their lawyers?*

It is important for those health professionals using nutrition to be clear that nutrition should not be used to *fight disease* but rather to *promote the causes of health and balance* in the body. To have healthy people we need healthy food, and to have healthy food we need healthy soil and farming systems.

In their paper to the legislative committee, RDs cited one "giveaway" of health frauds and quacks was the use of the word "alternative." Here, the RDs, perhaps as loudly as they can proclaim, reveal that they would be better off in the pre-Gorbachev communist bloc where the State does not allow any presence or even the concept of "alternatives." Yes, alternative is a particularly American concept, and one that Americans have died all over the world defending. It is the inalienable right of an American to search for a different and perchance better way of doing something. The word "alternative" is a cherished word to lovers of freedom and a hated and frightening concept for anyone who needs the cold monopoly of the State to intervene on their behalf because the free marketplace of goods, services, and ideas is not responding to their advantage. Try to think of a single area of human function where the "alternative" was not the factor that led to the betterment of humankind. Kings and princes do not like alternatives; Americans demand them.

"Eternal vigilance is the price of freedom" is a dictum that should be constant in the mind of a free people. James Madison knew that when he forced the delegates to include the pivotal ninth amendment to the Bill of Rights. That's the one that says that the rights that the government obtains through the Constitution cannot be used to take away the rights of the people, enumerated in the Bill of Rights or not. The right to seek the counsel of anyone we choose, in any matter we choose, is the right to be called an American. The filthiest word in the English language, the word that brought down the Communist experiment, is the word *"monopoly."* It fouls the soul and clouds the mind and blinds the people to the betterment that evolves through a free selection of goods, services, concepts, and ideas. At the current rate that ideas and concepts and knowledge are changing on a global scale, everything should be printed in pencil, and textbooks would be most appropriate in a looseleaf form. No, we don't need laws that limit and grant cartels. These times, more than ever, call for an increasingly impartial access to all information that can lead to wise choices.

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Estrogen in 1990

Editor:

The Magic of Estrogen Therapy

A stage magician can produce surprising illusions by directing the audience's attention to where something is not happening, or to a distracting gesture. The billion-dollar estrogen industry has learned the trick of directing the public's attention to where some plausible benefit might be expected, and of politely ignoring the areas where death and destruction are in fact being produced.

Interestingly, another billion-dollar industry - the edible oil industry - is using the same prestidigitation to profitably misinform the public. Decades ago, unsaturated oils were found to lower cholesterol. However, studies showed that adding the polyunsaturated oils to the diet didn't prevent death from heart disease, but that it did increase cancer deaths. There were also warnings that the oils could cause problems with blood clotting. There was silence from the industry, the government, and the medical profession in response to the bad news.

When evidence of an association between blood lipids and heart disease was found, the blood tests, rather than actual health, became the focus of publicity. A high ratio of HDL (high density lipoprotein) to LDL (low density lipoprotein) came to be identified with "health," because of its association with lower risk of heart disease, although it was also an indicator of a risk of death from cancer. By ignoring everything but heart disease, it could be argued that "If high HDL equals health, and estrogen and PUFA (polyunsaturated fatty acids) cause HDL to increase, then these things promote health."

Concerning estrogen, similarly twisted reasoning led to its trial in the 1960s to prevent heart attacks in men, but the experiment was stopped when the rate of heart attacks increased sharply.

Focus on the positive. Ignore the HDL-cancer association. Ignore the association of estrogen with thrombosis, embolism, stroke, edema, obesity, depression, myocardial infarction, eclampsia, epilepsy, brain damage, and immunodeficiency. Ignore the implications of thyroid suppression.

In her comedy routine, Judy Tenuta describes a most implausible situation, and then belligerently pleads: "It could happen; it could happen." The ignorance or mendacity which allows experts to plead the importance of one possible benefit, in the face of clear evidence of a multitude of serious dangers, defies any sort of conventional scientific response.

The recent corruption scandal involving the FDA's generic drug division might come to mind when I suggest that Tenuta's satire illuminates the attitude of the FDA (and the medical industry), but I believe the indictments are part of the prestidigitation.

Marvin Seife, who was head of the generic drug division, was indicted for perjury. The indicated intent of Congress had been to support generic drugs to break the monopoly of the biggest drug companies; but for the last six years there has been an intense campaign by the monopolies to keep generic drugs off the market, and Seife's indictment must be evaluated in this context.

Earlier, an FDA official who was too friendly toward DMSO and its developer, Dr. Jacob, was exposed for accepting a loan from the doctor. While keeping new entrepreneurs from intruding into the fabulously lucrative drug business, those little prosecutions allow the public to believe that the government is policing itself. (If your corporation could expect an additional $4,000,000,000 in profits in the next 10 years, but only if a few men would narrow the scope of their judgment, how do you suppose you could encourage those few men to go in the right direction?)

Just One Problem: Clots

Forty-five years ago the Shutes found that estrogen promotes the clotting of blood. At the same time, Knisely was studying the phenomenon of "blood sludging," which occurs under many types of stress. At that time it was recognized that there is an equilibrium between clot formation and clot removal (fibrinolysis).

Vitamin E and magnesium and some substances produced by the body shift the balance away from clots. Estrogen, calcium, altered water content and blood volume, and sluggish flow of blood encourage the formation of clots. Some contemporary articles acknowledge that estrogen can cause thrombophlebitis or thromboembolism and can exacerbate gallbladder and liver disease and breast cancer, but these warnings are subordinated to praising the benefits of estrogen replacement therapy. (Valery Miller, Veronica Ravnikar, and Chrystie Timmons, "ERT: Weighing the risks and benefits," *Patient Care*, 30-58, June 15, 1990.)

Some quotations from the ERT article by Miller, et al., illustrate current medical attitudes.

"Although the reasons for its apparent protective effect on the heart are not fully understood, oral estrogen does decrease low-density lipoprotein cholesterol and increase high-density lipoprotein cholesterol.

"Although no prospective study has yet shown that estrogen protects against cardiovascular disease, other studies show that women who use estrogen or who have ever used estrogen have a reduced risk of heart disease. The only study that has not confirmed these results is the Framingham Heart Study, which contained smaller numbers of older women and classified chest pain - a notoriously poor identifier of heart disease in women - as a cardiovascular end point." (p. 47)

The prospective long-term Framingham study noted above used to be highly praised as a source of reliable information on heart disease. In contrast, some of the studies that are praised in prestigious journals are wildly unscientific. For example, the heart disease in Marin County women receiving estrogen has been compared with that of women in the East Bay not getting estrogen. Marin County is a rich residential area, which is swept by ocean breezes while across the bay there are more working class people (and working class men are known to have nearly 50% more heart disease than white collar workers), and the wind from one direction blows smoke from a concentration of industries and refineries, from another direction it carries the pollution from San Francisco's traffic, and from another direction it brings the agricultural poisons of the Salinas area.

If enough women die from strokes, pulmonary embolisms, accidents, suicide, cancer, and loss of immunity caused by estrogen excess, it is possible that some competent study will eventually show that estrogen treatment reduces the mortality from heart attacks, but this is not likely.

It is the estrogen in oral contraceptives which correlates with their effects on the clotting system. *In the last 20 years there has been general agreement that increased risk of cardiovascular disease, rather than cancer or immunodeficiency or depression, is the most important concern about the effects of oral contraceptives.*[1-11]

There are many ways that estrogen can contribute to a hypercoagulable state (leading to cardiovascular disease). Some of these involve altered liver function, including disturbed production or metabolism of 8 different coagulation controlling factors.[12,13] Since estrogen can stimulate endothelial proliferation (often

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cited as crucial in heart disease) and reduces the rate of venous flow,[14,15] it is necessary to consider the whole complex circulatory system, and not just the clotting factors.

The thyroid and other hormones such as insulin and adrenalin are influenced by estrogen, and must be taken into account. Although I'm not sure what clinical perceptions led the Shutes to study estrogen's affect on clotting, pregnancy and lactation are notoriously associated with hypercoagulability (eclampsia and thromboembolism, for example) produced by the body's high estrogen production at those times.[16-23] The very high doses of estrogen that were once used to suppress lactation were found to produce clotting problems.[24] Postmenopausal use of estrogen causes changes in coagulability.[13,25,26]

In the mid-1970's when I pointed out that menopause resembles Cushing's syndrome[27] I hadn't investigated that disease of cortisol-excess enough to know the full extent of the parallel: for example, hot flushes, night sweats, and insomnia, such common menopausal symptoms, are also common symptoms in Cushing's syndrome. Estrogen's tendency to increase cortisol production should be considered in connection with the brain-aging effects of both estrogen and cortisol.[28,29]

Both estrogen and cortisol weaken the structural components of tissue, and the bruising which is so commonly associated with the premenstrual syndrome seems to involve the unopposed action of both of these hormones. The women who often have bruised thighs in their twenties are later susceptible to hemorrhages into the white part of the eye, and still later to bleeding into the brain, presumably because there is a hierarchy of protection against the tissue-weakening effects of those hormones, with the brain being the last to lose its resistance.

For example, the brain content of progesterone, pregnenolone and DHEA is normally 20 or 30 times higher than the serum concentration, and these hormones are protective against both estrogen and cortisone. As far as I know, it is possible to have fragile blood vessels at the same time as an excessive tendency to clot, though when the vessels break, the extent of the bleeding will be smaller in the hypercoagulable state. The observation that low cholesterol is associated with increased risk of hemorrhagic stroke[30] suggests that the age-related decline in progesterone, pregnenolone, and DHEA occurs earlier when there is a low level of the precursor substance, cholesterol.

Clotting too easily is just one of the problems that can be caused by an excess of estrogen, and I don't mean to give it too much emphasis, since I consider its toxic effects on the brain, and its acceleration of brain aging to be its worst effects - though its cancer inducing effects on the uterus, the breast, the lung, the bowel and liver, and brain, are certainly serious. But in 1990, estrogen's cardiovascular toxicity is probably the aspect that people need to be reminded of.

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Hair Analysis

Continued from Page 18

It's nonsense like this that gives the field of hair analysis its shady reputation. I'm afraid that as long as hair analysis laboratories continue to offer their services to an unsupervised, untrained general public and continue to write suggested diagnoses in their printouts there will continue to be heavy criticism of the whole field. And deservingly so! Hair analysis laboratories will have to unlock themselves from the mentality of doing these things as well as recommending supplements before they can earn the respect of responsible physicians and medical associations. Rather than criticize the data in Dr. Barrett's article further, I think the representatives of Doctors Data Inc. and Trace Minerals International would be better off in the long run to seriously consider cleaning up the rather messy field of hair analysis first.

Despite the many drawbacks and irreproduceable results of many accredited blood testing facilities, these laboratories have a great more credibility than those offering hair analysis simply because they only accept samples from licensed practitioners. Blood testing laboratories have quality control standards to abide by as well as other professional standards to comply to. In Canada, at least, all blood testing laboratories are closely scrutinized by government and other health protection licensing bodies. Licenses are frequently lifted if the labs don't "measure up." If this sort of scrutiny was applied to hair analysis laboratories, I very much doubt there would be any more articles like "Commercial Hair Analysis, Science or Scam?"

I sincerely hope that the hair analysis industry takes this criticism as something to learn from rather than something to be defensive about. After all, hair analysis, done correctly and interpreted together with other clinical data (patient history, dietary analysis, physical examination and blood and urine tests) provides some very useful data about the health of a given patient that could not as easily be determined by other means. In particular, in the area of heavy metal overburdening (especially lead and cadmium), hair analysis is superior, as an early warning screening tool, to blood or urine testing. Let's not spoil it with unprofessional application and nutritional supplement profiteering.

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Asthma and Metabisulfite

Editor to *J.A.M.A.*:

An asthmatic friend of mine had several experiences of getting sicker when she was medicated for asthma. While hospitalized, her doctor insisted on giving her Alupent. After she left the hospital, she showed me the Alupent label and asked if I knew why it would make her so sick. The label listed metabisulfite as an ingredient. Since this substance is known to cause trouble in asthmatics, it is very odd to find it in an asthmatic drug.[2] I don't find metabisulfite listed as an ingredient of Alupent in the PDR or other drug manuals, and the physicians I have mentioned it to were surprised. Sudden death from "paradoxical bronchospasm" would not be paradoxical at all.

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Reference

Towns SJ and CM Wellis, Acetylsalicylic acid and sodium metabisulfite in chronic childhood asthma, *Pediatrics* 73 (5): 631-637, 1984.

Dear Doctor Peat:

This will acknowledge your letter of August 24, 1985. I regret that in view of the many submissions we receive and the premium on space, we were unable to assign the necessary priority to the letter for publication in the *Journal*. We have forwarded your letter to Boehringer Ingelheim, Ltd., and asked them to respond to you directly.

Drummond Rennie, M.D.
Editor, Letters Section
JAMA
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Dear Dr. Peat:

Thank you for your interest in Alupent® Inhalant Solution 5% brand of metaproterenol sulfate. Dr. Drummond Rennie, Editor of the Letters Section, *Journal of the American Medical Association* advised us that you are concerned with its use as a bronchodilator in the asthmatic population since this product contains sodium metabisulfite.

The use of sulfiting agents as food and drug additives has recently been found to be responsible for adverse reactions which may result in life—threatening asthma and anaphylaxis (Jamieson D.M. et al., *Ann Allergy* 54:115-121, 1985). The generation of SO_2 by the reaction of sulfites with water can provoke bronchospasm in some patients (Tashkin D.P., *West J Med* 140 (1): 82-83, 1984). Paradoxical bronchospasm can occur following the administration of aqueous inhalant solutions containing the metabisulfite preservative, although whether this phenomenon is actually due to the presence of metabisulfite, is uncertain.

Koepke et al. (Koepke J.W. et al., *J Allergy Clin Immunol* 72 (5):504-508, 1983) observed experimentally that a significant amount of SO_2 was released during standard nebulization of four commercially used bronchodilators, vis-a-vis Isoproterenol, metaproterenol, isoetharine, and racemic epinephrine. The SO_2 concentrations varied from 0.1 to 6.0 ppm which can induce broncho-constriction in asthmatic patients. It was observed that metaproterenol solutions were associated with the lowest SO_2 levels with the least lot-to-lot variation.

In asthmatics, bronchospasm can be produced by as little as 5 mg of oral sulfite or by inhalation of 1 ppm SO_2 over 10 to 30 minutes. In nonasthmatics, bronchospasm can be caused by inhalation of SO_2 in a concentration of 6 ppm (Jamieson D.M. et al., *Ann Allergy* 54:115-121, 1985).

The incidence of metabisulfite sensitivity in a random asthmatic population has been found to be 8.2%: five of 61 asthmatics without history of metabisulfite sensitivity who received oral challenges developed bronchospasm (Jamieson D.M. et al., *Ann Allergy* 54:115-121, 1985). Hypersensitivity reactions to sulfites are unpredictable and the severity will vary with the degree of airway irritability and the sulfite concentrations in foods or drugs (Twarog F.J. and Leung D.Y.M., *JAMA* 248 (16): 2030-2031, 1982). There are insufficient data to indicate which doses are most likely to evoke reactions in sulfite-sensitive individuals. However, it has been found that sensitive asthmatics may develop bronchospasm during exercise from inhaling as little as 0.1 ppm of SO_2 (Jamieson et al., *Ann Allergy* 54:115-121, 1985).

ALUPENT® 0.6% Inhalant Solution Unit Dose Vials do not contain sodium metabisulfite. In the near future, subject to FDA approval, we plan to market a reformulated ALUPENT® 5% Inhalant Solution in which sodium metabisulfite is replaced by a different preservative.

We take pleasure in enclosing a selection of articles pertaining to metabisulfite sensitivity and hope you will find this information useful. Please do not hesitate to contact this department whenever we can be of further assistance.

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Cellular Therapy Not Legal in Nevada

Editor:

I believe a retraction is in order concerning the alleged legalization of Cellular Therapy in the State of Nevada.

According to the information this Clinic has received from Mr. Elliot King of the Nevada State Board of Pharmacy, who approves any and all drugs used in the State of Nevada, there has been no legalization of cell therapy in the State of Nevada.

I do know that American Biologics has prepared and done extensive research in cell therapy and is using cells specially made in Mexico under clinical standards. We have sent many patients to Mexico for this kind of therapy and if it were legal, we would be doing that treatment here in Las Vegas.

We have also learned that several legislators and the wife of a highly placed official in Nevada has been taking cellular therapy, in Nevada, with imported material which is not legal.

We do propose at the next Nevada Legislature that we shall present the excellent research done over the past three years by American Biologics in Mexico and request the Legislature to place the same standards as are placed on Laetrile and Gerovital — that is, the drug be

Continued Next Page

Homeopathy, *Continued from Page 271*

of the doctor and his staff in eliciting comprehensive and complete information from the patient. Any experience—physical, emotional, or mental—plays a part in the health condition. The individual's history constitutes important information, not just physical ills, but also living circumstances.

A well-organized patient who prepares information prior to arriving at the doctor's office, and a well-trained staff that ensures the information is complete, will enable the doctor to spend his time with the patient elucidating the nuances and subtleties that will help him match the conditions observed in the ill patient with those given in homeopathic references as caused by particular substances.

The fundamental references for this matching process are the repertory and the materia medica. The repertory follows a format that lists parts of the body and the symptoms associated with them, plus descriptions of mental and emotional states. With each observed condition appears the name of one or more homeopathic medicines known to cause those symptoms in a healthy person. The physician then proceeds to list the names of relevant medicines associated with each symptom until he has collected a comprehensive profile of as many of the patient's symptoms as possible. Then, he must observe which of the homeopathic medicines occur most frequently, and use his intuition to select the medicine most likely to act as the similimum to the person's condition.

Generally, this methodical approach approximates the ideal more than the average work up for a patient. After all, there are more than 2000 homeopathic medicines! It is usually followed in its entirety only with chronic conditions, rather than acute. For acute conditions, a number of medicines will share common symptoms and are known as "polycrests." These will encourage the body and accelerate the cessation of discomforting symptoms. What is best about the homeopathic alternative: no side effects and no sense of "drugging."

Homeopathic medicines marketed as "combinations" are available in health/natural food stores. Generally, the bottle carries a label for a particular symptom picture, such as sore throat, varicose veins, etc., and consists of a group of polycrests, sometimes up to six together and always in low potency. Higher potencies usually come into play when the symptom picture is clear and the similimum seems apparent.

The other fundamental reference for the physician's use is the materia medica. This type reference lists the medicine, or substance, and the symptoms associated with its action in a healthy person. It is the documentation of the "provings" described above. In fact, the materia medica serves as the basis for the repertory, along with the clinical experiences of the compiling physician.

How to get started?

Currently, no accredited medical schools offer courses in homeopathy. However, a number of institutions and individuals do offer courses for physicians that can enable them to introduce homeopathic techniques and medicines into practice on a gradual, progressive basis. In addition, many good books written by practitioners *for* practitioners exist.

For further information on what to read and on study opportunities, contact: United States Homeopathic Association; 5305 Lee Highway; *Arlington, VA 22207; (703) 534-2600.*

Reprinted from AMERICAN HOMEOPATHY /Consumer Edition, February, 1984.

Immunity, Hormones and Yeast Infections

by Ray Peat, *Ray Peat's Newsletter*

In understanding candidiasis, two things, related to each other, are of special importance: the involvement of the endocrine system, and the suppression of natural immunity. Similar endocrine and immune problems can occur in other situations: cancer, aging, viral infections, and chemical poisoning. Damaged cellular respiration appears to be the common mechanism. A skin test, using Candida antigen, based on the universal exposure and acquired immune reactivity to it, shows a similar lack of response in both systemic candidiasis patients and in cancer patients. In a study of cancer patients, nutritional supplementation increased skin reactivity and survival. According to R.A. Cox, anergy of the cell-mediated immunity and a T-cell deficiency are found in chronic mucocutaneous candidiasis. In 1860, Trousseau said that candidiasis is "the local expression of a very bad state of the whole system." Similar observations have been made regarding cancer and tuberculosis.

> Thyroid, progesterone and pregnenolone help to normalize blood sugar by improving respiration, and should be the basic treatment for allergies.

Another surprising similarity between candidiasis and cancer is that the antibody reaction might be harmful, rather than helpful. According to Diamond, "high levels of specific antifungal antibodies may sometimes block or inhibit the development of cell-mediated immunity to mycoses."

Simplified ideas of the immune system were fostered by the success of vaccination against certain diseases, and by the preference of most researchers for clearly defined single-level mechanisms. Influences from the environment, nutrition, hormones, and biological rhythms make the problem more complex, but few people have recognized the importance of nonspecific immunity and the organism's general resistance. Early in this century, light therapy was recognized to be effective for tuberculosis. Coley's toxins were another early and successful attempt to stimulate the immune system. W.F. Koch, working in Gomberg's lab with free radicals, postulated that free radical oxidation was central to natural resistance to infection and cancer. Similar ideas were developed by Albert Szent-Gyorgyi, and many others contributed supporting evidence for the *importance of respiration in resistance to* disease—Otto Warburg, Max Gerson, and Broda Barnes, for example.

The two hormones, estrogen and cortisone, are associated with stress, with respiratory changes and with changes in the immune system.

A recent review article by C.J. Grossman (*Science*, Nov. 30, 1984) outlines the effects of estrogen on the immune system. Estrogen causes atrophy of the thymus, and depresses the circulating levels of thymosin alpha one: when estrogen is given to castrated rats, their serum has "a marked inhibitory effect on T-cell function," and "estrogen and androgen act mainly to suppress the cell-mediated immune system." Estrogen increases antibody production, which is not necessarily helpful in conditions such as candidiasis and cancer. Estrogen retards skin graft rejection, and this probably indicates how parasites will be handled.

An especially important effect of estrogen is its reduction of the amount of IgA antibody secreted at membranes—this is very likely to be the reason for the high incidence of vaginal yeast infections premenstrually and during pregnancy. Thyroid and progesterone both increase the secretion of IgA, and these hormones are frequently deficient premenstrually and in pregnancy.

Allergy and epilepsy consist of hyperactivity of, respectively, immune cells and nerve cells. Low cellular energy, caused by hypoglycemia or hypoxia, causes hyperactivity of any cell type; the easiest way to observe this phenomenon is in the delayed relaxation of a hypothyroid person's Achilles reflex, or a delayed repolarization wave in the electrocardiogram. Estrogen interferes with cellular energy in many ways, including a contribution to hypoxia by impairing oxygen absorption. Thyroid, progesterone, and pregnenolone help to normalize blood sugar by improving respiration, and should be the basic treatment for allergies.

Some fungi have been found to respond to the human sex steroids, estrogen and testosterone, and there is evidence for a corticosteroid receptor in Candida (D.S. Loose, *et al.*) suggesting that the yeast produces and responds to a hormone resembling cortisone. Estradiol, the most powerful human estrogen, has been extracted from a yeast (A. Burshell, *et al.*, 1984).

For many years, male beer drinkers have been known to develop breasts. Since liver damage causes abnormal amounts of estrogen to be produced and retained, the alcohol was blamed, but in the last year, enough estrogen was found in beer and wine to account for the condition, independently of any alcohol damage to the liver. Bread was also found to contain significant amounts of estrogen, from the yeast. (The increased rate of cancer which has been observed in beer drinkers might have something to do with estrogen. It would be interesting to compare the cancer incidence *among bread eaters with the incidence in peo*ple who eat tortillas, pasta, or potatoes.)

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Immunity, *Continued from Page 273*

Since early in this century, brewers' yeast was used for treating diabetes. The pancreas has an estrogen receptor, and estrogen promotes insulin secretion. Since reading of yeasts' responsiveness to sex hormones, about 15 years ago, I have encouraged people to use liver when they need a vitamin-mineral supplement, and to restrict the use of brewers' yeast mainly to the treatment of diabetes.

Besides people who are debilitated from starvation, drug treatment, or old age, the main groups who have a high incidence of Candida infection are diabetics, pregnant women, and premenstrual women. Rosalinde Hurley lists susceptible conditions, including infancy, severe infections, leukemia and other defects in cell-mediated immunity, and endocrine disease; she also mentions that the unhealthy skin near ulcers is often colonized by Candida.

A high glucose concentration in body fluids would be an obvious factor in diabetics, and in some pregnant women, but blood sugar tends to be low premenstrually. Many diabetics have high levels of cortisone, and some women do in pregnancy or premenstrually, but the consistent feature of pregnancy and the premenstrual part of the cycle is an increased production of the sex steroids.

Since progesterone used to be called the "luteal hormone," many doctors have wrongly associated it with many premenstrual events, including water retention. Most medical textbooks make the same mistake. The corpus luteum secretes both estrogen and progesterone, and when the person is under stress, progesterone production fails, while estrogen secretion continues. Progesterone deficiency and estrogen excess very often occur in the "luteal phase," premenstrually, and in pregnancy, and at menopause, with symptoms such as edema, emotional disturbances, blood clotting problems, and allergy symptoms. I think this misconception, that progesterone is "the luteal phase hormone," rather than the often deficient protective hormone, is what caused Dr. Truss to warn against its use in candidiasis patients. (Since most doctors prescribe synthetic progestins, with estrogenic and androgenic side effects, instead of natural progesterone, Truss's warning has probably helped some women to escape that maltreatment.) Because of its effects on IgA, on blood sugar and the allergic reaction, and on the body's response to stress, natural progesterone would seem to be one of the most useful materials in treating candidiasis.

In the fungi which respond to the human sex steroids, these hormones function as sex hormones, or as sex pheromones—they attract the appropriate cell type, while causing changes in the cells which prepare them for conjugation.

In cell culture, virulent strains of Candida were found to adhere to cells from human membranes, while non-virulent strains didn't adhere. Also, the virulent forms of yeast adhered to cells taken from some people, and didn't stick to cells from other people. Even *in vitro*, vaginal epithelial cells were more attractive to Candida—more yeasts adhered—when cells were from diabetics, pregnant women, or women near menstruation. This strongly suggests that glucose is not the regulating factor, since the glucose would be standardized in the culture fluid. More likely factors are estrogen, cortisone, the absence of an iron binding protein, or of bound antibodies; hypoxia causes increased cellular concentration of free fatty acids, so this is another possible factor.

The obvious next experiment will be to pretreat both yeast and donor cells with estrogens and other hormones including cortisone and testosterone, to see if virulence can be induced.

Estrogen and cortisone are things which suppress the host's immunity, and which appear to modify the fungus. Two other things, which have interesting connections with estrogen, can suppress immunity and stimulate yeast growth: unsaturated fatty acids and excess iron. Diamond has suggested that the reason candidiasis often occurs in leukemia is the high iron level in that disease; others have suggested that leukemia itself might be caused by an excess of iron, blocking the immune system. Iron (and high levels of zinc, i.e., 10mM) stimulate the formation of mycelia (Hazen and Cutler, 1983).

In a low oxygen environment, unsaturated fatty acids can stimulate yeast growth (Nes, *et al.*, 1984), and they suppress immunity in various ways.

Besides a direct effect on cellular immunity, unsaturated fatty acids interfere with thyroid function and with mitochondrial respiration. Low thyroid leads to high estrogen. Estrogen (and low thyroid) cause increased absorption of iron. At an extreme point, excess iron disturbs several endocrine glands, but at a more moderate level, it blocks cellular immunity. Combined with unsaturated fatty acids, iron stimulates peroxidation, with toxic effects, including the formation of carbon monoxide, inhibiting respiration. Vitamin C stimulates the absorption of iron, and can also increase the rate of peroxide formation. In a special disease of iron retention, idiopathic hemochromatosis, vitamin C was found *not* to increase iron *excretion* when tested by itself, though it did increase the effect of a drug called deferrioxamine (D. Conte, *et al.*, Acta Haematol. (Basel) 72(2), 117-120, 1984).

The mitochondria are not only the site of respiratory energy production, but are where cholesterol is converted to pregnenolone, which is then converted to progesterone and DHEA. These steroids all appear to protect the respiratory system. This respiratory protection is probably part of what Selye called the "catatoxic" function, the fact that certain steroids, especially pregnenolone, protect organisms against a great variety of poisons.

Whether it is an exogenous chemical, or a poison produced by intestinal organisms, or a toxic effect of damage to one's own tissue, which is making a person sick, it would seem reasonable to use a protective, "catatoxic," material such as pregnenolone as part of the supportive therapy. Fiber, oxygen drinks, and aspirin can protect the bowel.

My first experiments with yeast were with the Koch reagents, but then I got interested in testing possible anti-iron substances. Caffeine, I suspect, uses that mechanism, among others. I have also experimented with essential oils, clove oil, thymol, and menthol, and elemental sulfur, which is probably the least toxic therapy for many fungus infections of the skin, vagina, and bowel. Lime-sulfur and other sulfur mixtures have a long history as fungicides. Saturated fatty acids generally inhibit fungal growth. Short chain acids, such as acetic, lactic, propionic, and caprylic acids have often been used as anti-fungals, and even the longer chain saturated fatty acids have been tested.

Large doses of vitamin A and potassium iodide have been used, separately and together, to promote general immunity, and also to treat fungus infections; I suspect that an effect of the iodide is to protect against the toxicity of the unsaturated fatty acids.

Thiosulphate is another form of sulfur that has been used for skin fungal infections. Many herbal drugs contain quinones and saponins, which are active against fungi, but which can be dangerous to the patient. The imidazoles can be dangerous, because they block steroid synthesis in the patient as well as in the fungus. Nystatin is also believed to act on fungal steroids, and it can be toxic to the patient, but it is considered the best treatment for a deadly systemic infection (e.g., lungs, heart, kidneys). Desensitization with Candida vaccine and treatment with immune rabbit serum are discussed in R. Dubos's book, *Bacterial and Mycotic Infections of Man*. Boric acid (5%), antihistamines, and many other chemicals have some anti-fungal activity, but except for sulfur, I think the best approach is to optimize the patient's resistance.

Ray Peat's Newsletter, P.O. Box 3427, Eugene, OR 97403.

Chilies Chase Chills

With a heading, "Chilies Chase Chills," an article in the February, 1983, *American Health* magazine encouraged its readers to eat spicy food for health enhancement. Dr. Irwin Ziment, Professor of Medicine at U.C.L.A., indicates that by stimulating mucus flow, spices can help prevent and treat respiratory problems such as asthma, bronchitis, sinusitis and colds.

Dr. Ziment says, "The reason most people with chronic lung disease have problems is because abnormal mucous secretions get stuck in the lungs. We want to stimulate the lungs to produce watery secretions to loosen the mucus in the airways." Dr. Ziment doesn't address the potential cause of the excessive mucus production, which could be attributed to, among other things, food sensitivity.

It is believed that hot foods irritate the digestive tract, and cause a reflex increase in secretions from the nose and lungs. "People who eat spicy foods have less chronic obstructive lung disease than people who don't," Ziment says. He recommends that his patients with bronchitis eat one spicy meal a day, and drink lots of water. For those with G.I. tracts that can't handle such zest, Ziment suggests gargling a cup of warm water mixed with 10 drops of tabasco sauce!

Aromatic herbs, in general, are believed to act as a preventative to many ailments by insuring more complete assimilation of food nutrients. Ben Charles Harris in *Better Health With Culinary Herbs* notes, "The herb's alkaline salts combine with its aromatic principles or volatile oils and work to conteract the fat or catarrhal-forming principles of many foods." He notes that thyme has long been used in bronchitis with an age old reputation to "drive forth phlegm," an action confirmed by the U.S. Dispensatory.

European AIDS Research Ignored

by *Fr. Richard Wilhelm*
Spotlight Newspaper

Dr. Horst Keif is curing AIDS victims in the Munich area of West Germany, by hyperoxygenating their blood with ozone, which destroys the AIDS virus on contact.

The same basic process appears to be also effective against hepatitis, herpes, the Epstein Barr virus and the cytomegalovirus, as well as providing a simple method of purifying stored blood and blood components, and preoxygenating blood to be transfused. Some of the medical uses of ozone have been appreciated for years in Europe and elsewhere but are still relatively unknown in the United States.

The treatment itself is remarkably simple: The ozone is produced by forcing oxygen through a metal tube carrying a 300-volt charge. A pint of blood is drawn from the patient and placed in an infusion bottle. The ozone is then forced into the bottle and thoroughly mixed in by shaking gently, whereupon the blood turns bright red.

As the ozone molecules dissolve into the blood they give up their third oxygen atom, releasing considerable energy, which inactivates all lipid-envelope virus while leaving blood cells unharmed.

Ozone overcomes AIDS virus by a fundamentally different process than usually attempted with drugs. Instead of burdening the liver and immune system with more elaborate toxic substances, ozone simply oxidizes the molecules in the shell of the virus, rendering it incapable of spreading.

It also oxygenates the blood to a greater degree than is usually reached, what with poor air and sluggish breathing habits. The treated blood is then given back to the patients. This treatment is given from twice a week to twice a day, depending on how advanced the disease is. The strengthened blood confers some of its virucidal properties to the rest of the patient's blood as it disperses.

The disease will not return, as long as the patient maintains his blood in an oxygen-positive state, through proper breathing, exercise and diet.

Research Ignored

The major U.S. news media and the medical Establishment seem to be ignoring this line of research. Meanwhile hundreds of millions of dollars are being spent to "try to find a cure," which supposedly won't be available for years, if ever.

Once AIDS is diagnosed, "it means death," insists American Medical Association (AMA) President Dr. John J. Coury. "There is no cure...and no immunization."

He also mentioned that each case brings the medical industry another $40,000 to $150,000, or 40 to 150 million dollars from every thousand victims. Of course, that's totally unconnected with the AMA's silence about the AIDS cases cured with ozone.

Apparently the lone exception to the medical Establishment's overall lack of interest in this promising breakthrough is the Food and Drug Administration (FDA) approval of the Medizone Co.'s tests on ozone blood treatment.

The New York-based company obtained an "investigative new drug" approval for ozone, which falls under the heading of "drugs" even though it isn't. Their recently completed animal tests have demonstrated no indication of toxicity, at 10 times the equivalent amount that is proposed for human treatment.

Medizone was granted U.S. Patent No. 4,632,980 on December 30, 1986, on "inactivating lipid-envelope viruses in blood that is returned to a mammalian host."

In humans, this includes AIDS, herpes, hepatitis, Epstein Barr virus and cytomegalovirus.

Medizone now has FDA approval to begin human testing.

All this has been with virtually no publicity, because the accepted procedure for publishing medical breakthroughs is to complete all the tests first, even though victims may die waiting for the cautious, methodical testing procedure to run its course. No one in the industry wants to raise false hopes, let alone repeat the medical disasters that have resulted in the past, from rushing approval on new treatments.

On the other hand, the drug AZT was widely publicized for many months before it was approved in the United States, as is ongoing research into possible AIDS vaccines.

The difference is that ozone offers an actual cure, and it's cheap.

AZT does not cure but only buys time, and is expected to cost $10,000 per patient per year, bringing the Burroughs-Wellcome Co. up to $300 million, from the 30,000 reported AIDS cases.

Information given here is for research and educational purposes only and is not intended to prescribe treatment.

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Ray Peat's Newsletter

AIDS/Syphilis Treatments & Ideas

Two of the best articles on AIDS that I have read are by Katie Leishman in *The Atlantic* (August, 1987 and January, 1988). In the earlier article, she discussed some of the poorly publicized alternative theories about the cause of the disease, and presented some of the arguments about the method of transmission, especially about lice. In the January article, she concentrates on the association between AIDS and syphilis.

Leishman quotes the argument of Jean McKenna, of Berkeley, that the AIDS-associated virus, HIV, is a by-product of the disease, rather than its cause, and that it probably only infects someone who is already immunosuppressed. Reading the older scientific literature, McKenna learned that both Kaposi's sarcoma and pneumocystic carinii pneumonia had been associated with syphilis.

The literature suggested that syphilitic patients are prone to various opportunistic infections, as AIDS patients are, although syphilis does not appear to suppress the immune system until its latent and tertiary stages. She tested twenty-four HIV-positive subjects (most of whom were ARC and AIDS patients) with a documented history of syphilis.

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Although all of their FTA (fluorescent treponemal antibody) tests should have been reactive, twenty-one were not. McKenna speculated that all AIDS patients might have syphilis.

In 1981, before AIDS had been recognized, two German physicians, K. Dierig and U. Waldthaler, guessed that gonorrheal endocarditis might be causing a patient's hot flashes, drastic weight loss, shortness of breath, and confusion, so they treated him with 40 million units of penicillin intravenously each day for three weeks. His symptoms disappeared, and later they found he tested positive for HIV, and a review of his 1981 laboratory tests "showed abnormalities consistent with AIDS." Dierig and Waldthaler then used the same penicillin treatment on six other ARC and AIDS patients. All seven are now "clinically asymptomatic." (The usual treatment for syphilis in the US is a single injection of 2.4 million units of benzathine penicillin. This form of penicillin does not penetrate the brain. In some countries, syphilis is treated for a year.)

Leishman also describes the work of Salvatore Catapano, of Valley Stream, Long Island. Thirty years ago, Catapano learned that the Enterobacteriaceae stimulate immunity, and found that typhoid vaccine could stop the growth of tumors. When he saw patients with Kaposi's sarcoma, he was reminded of syphilitic sores he had seen in the tropics. Catapano believes that the tropical spirochetal disease, yaws, shouldn't be considered as a distinct disease. He advocates the use of typhoid vaccine to stimulate the immune system before treating AIDS patients with penicillin. Catapano also believes that "syphilis" infections can occur without the presence of a spirochete, possibly by a virus-like variant of the organism. This idea has been proposed many times, e.g., by Bergel, in *Syphilis im Lichte neuer Untersuchungen*, Jena, 1925.

A few months ago, D.J. Bauer of Wellcome Laboratories, wrote an article on the history of antiviral drugs. I know of his 1959 work, in which he showed that copper inhibited the growth of a lipid-coated virus in the brains of mice, so I was surprised to see that he didn't mention copper or zinc, and that his story began with the introduction of amantadine in 1964 to treat influenza (which, like herpes and HIV, is also lipid-coated). I had been interested in amantadine for a long time, because it modifies nerve function in a way (anti-cholinergic) that I think mimics certain steroid hormones which I consider to be part of our natural anti-viral defense system. So I was also surprised to see that Bauer gave no explanation of the origin of amantadine.

Amantadine (or adamantaneamine) is a water soluble form (1-amino-adamatane) of a substance that occurs in petroleum. I noticed that adamantane smells like camphor, and that it has a cage-like shape which is very much like that of camphor. Camphor has a long history of use as a germ-killer (e.g., Campho-phenique, for herpes), and was used successfully in the great influenza epidemic 70 years ago. I assume that the idea of using amantadine to treat influenza was based on its obvious similarity to natural camphor. An oxidized form of camphor, camphoric acid, also has a faint odor of camphor, and has been used as an oral germ-killer. It was tested as a syphilis treatment in comparison with penicillin and the traditional arsenic compound, salvarsan, shortly after penicillin became commercially available. All three eliminated the syphilis infection, but the drug companies were already set up to produce large amounts of penicillin profitably. Camphoric acid was used to carry bismuth, another heavy metal that was effective against the syphilis organism. (I was interested in using camphoric acid to transport copper, making it able to enter the brain and also causing it to be absorbed via the lymphatic system, by-passing the liver and thus allowing a large dose to be absorbed without injuring the liver. I swallowed a small amount, and the next morning, noticing that my mouth felt fresh when I woke up, found that my tongue didn't have its customary coating. I have heard that harmless spirochetes tend to grow on the tongue).

Infection with the "trench mouth" organism, Trepenema Vincenti, was often associated with a deficiency of white blood cells. Another spirochetal disease, Weil's disease, involved fever, headache, vomiting, and intestinal bleeding. Still another type of spirochetal infection was known in Mexico as "pinta," and mainly involved depigmentation of the skin. Early in the century, some of the abnormalities of pigmentation, teeth and hair development, and defects in blood vessels, that had been attributed to syphilis were found to result from a copper deficiency.

For at least 80 years, people have been observing an association between anesthesia and the elimination of viral infections. We have at least three natural anesthetic systems, namely, the GABA system, the endorphins, and the steroids (especially progesterone). These very likely are just three aspects of a single system. Close analogs of the GABA system are already known to have anti-viral action.

About 60 years ago, it was commonly believed that women, especially during pregnancy, are resistant to syphilis. Moore (*Johns Hopkins Hosp. Bull. 34*, p. 89, 1923) states that it is fair to assume that pregnancy is the factor which suppresses the lesions of the disease. The protection may persist over a long period of years and possibly for a lifetime. Spontaneous cure seems in a few instances to have been the ultimate result.

It seems necessary to believe that some substance produced in the course of pregnancy and non-existent in the tissues and body fluids of males and non-pregnant women is antagonistic to the spirochaetae, but whether this is derived from corpus luteum, or other organ of internal secretion, or from the placenta or foetus, is merely a subject for speculation. (W.G. MacCallum, *A Text-Book of Pathology*, W.B. Saunders, 1937, p. 684.)

Camphor, progesterone, nutritional supplements, and artificial fever have even fewer side-effects than penicillin, and should be tested more widely. The GABA analogs, besides being non-toxic, have the additional advantage of being very cheap. In the pharmaceutical-bureaucratic world, though, this has too often been a fatal defect.

The close association between immunity and the balance of iron and copper suggests that the iron/copper ratio should be studied in AIDS.2 The fact that hemosiderosis (a disease of excess iron absorption) occurs mainly in Africans and in transfusion recipients might be expected to relate to the virulence of any infectious disease in those populations. The tumor of Kaposi's sarcoma is often pigmented with hemosiderin. Although the suppressive effect of iron on the immune system is well-known, it is generally ignored, probably because of our society's obsessive belief that "iron is good for you." Iron's effect on the immune system is interestingly examined by June

• AIDS Campaign

Goodfield in *An Imagined World.*

Since I mentioned the endorphins above in the context of resistance to infections, I should mention that these endogenous peptides are really a family of substances with very different properties; some activate the right side of the brain, others activate the left side.3 The two sides of the brain have different effects on the immune system. Opiates are powerful suppressors of immunity.5 I think it is clear that morphine and codeine should never be used when there is an immune deficiency.

References

1. Serum copper rises sharply during pregnancy, partly as a result of high progesterone levels. Copper provides some protection against iron toxicity.
2. Physicians with AIDS or ARC patients are invited to participate in a study of these and other factors. The Health Discernment Laboratory in Santa Barbara, Calif., will do the serum testing. They will do tests on about 12 of each at no charge, but very special handling of the serum is necessary, and instructions are available.
3. Ye. Chazov, *et al.*, "Chemical asymmetry of the brain," *Science in the USSR*, No. 1, pp. 21-29, 1987.
4. P.J. Neveu, *et al.*, "Modulation of mitogen-induced lymphoproliferation by cerebral neocortex," *Life Sciences 38*, pp. 1907-1913, 1986.
5. H.U. Bryant, *et al.*, "Immunosuppressive effects of chronic morphine treatment in mice," *Life Sciences 41*, pp. 1731-1738, 1987.

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AMA NEWS

Register Publishes Clearinghouse Rules

by Diane M. Gianelli

Proposed rules related to the national clearinghouse for MD licensing and malpractice data were published in the March 21 issue of the *Federal Register.*

The rules – which detail the types of information that must be reported to the data bank, the entities that must report information, the conditions under which parties will have access to the confidential information, and the penalties for non-conformance – are subject to a 60-day comment period before final regulations are issued.

The clearinghouse, which also will include information on dentists and other licensed health professionals, was mandated by Public Law 99-660, the Health Care Quality Improvement Act of 1986. It was established to provide a central repository of information on health care providers so as to improve the quality of the nation's medical care by identifying those engaged in unprofessional behavior, and by providing a means to restrict incompetent providers from moving to other states to set up practices without fear of detection.

The data bank was scheduled to begin functioning last November, but funding has not yet been appropriated.

The American Medical Association and the Federation of State Medical Boards applied jointly for the contract to run the data bank, but because the eligibility period for consideration has run out, they will have to re-bid. Administration sources predicted that the data bank would not become operational before 1989.

Issues likely to be discussed by affected groups before the May 20 comment deadline will include procedures related to resolving disputes about the accuracy of information reported to the data bank. The proposed rules request comments on the subject, saying: "In light of the sensitivity of this information, we specifically solicit comments on how disputed information should be handled prior to settlement of the dispute."

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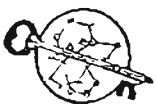

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cellular-toxicity, and organ-toxicity) using computer modeling with *in vitro* test systems based on biochemical methods using enzyme and tissue culture assays; and additional animal feeding studies using the radiation-induced chemical(s) (**RP** or **URP**) in question and *not* the irradiated whole food!

In my opinion, whole foods, irradiated under controlled, laboratory conditions, should only be employed for nutritional-biochemical and molecular biological studies in animals fed balanced and special diets consisting of these irradiated foods and the components and sub-components of the irradiated foods that are of concern.

Please introduce my **Proposed Research Plan** during your **WHO Consultation: Update on Food Irradiation** meeting. I believe this **Proposed Research Plan** will provide both a relevant context for analyses and discussions *and* a useful framework for identifying data gaps in the existing compilation of research performed to date; in addition, I trust this **Proposed Research Plan** will identify fruitful areas for future research. Also, please place my name on your mailing list to receive your publications and notices.

Thank you for your time and consideration of my request. If you have either comments or questions, please feel free to telephone me at home at any time - 415-712-8008 for discussions, messages, or FAX transmissions.

Jeffrey H. Reinhardt, M.Sc.
Consultant in Nutritional-Biochemistry
25 Mitchell Blvd., #8
San Rafael, California 94903

Failures of Immunity

Editor:

From ancient times until the 1940s, young adulthood was the healthiest phase of life, with an insignificant rate of death from disease. Septicemia, bacterial infection in the blood, had been associated with the natural immune deficiency of old age. By the 1960s septicemia was killing many young adults, in spite of the susceptibility of the germs to antibiotics.[1,2] The use of antibiotics did save enough immune deficient people from septicemia to allow an increasing incidence of other diseases, including Pneumocystis carinii pneumonia, to become apparent. Acquired immune deficiency (AIDS) was a recognized syndrome for many years, and it was known to be increasing long before the 1980s.[3]

P.H. Duesberg had made the point that most of the present AIDS epidemic can be explained by the various known causes other than the HIV virus. I think he is mostly right, but I don't exclude the possibility that the virus in itself could be a significant cause of the disease. My judgement would be that the virus is a "co-factor" in the disease, and by this I mean that we have been exposed to an increasing burden of immunosuppressive factors, which are causing an exponentially rising curve of immunodeficiency diseases, and that, arriving at a certain point on that curve, the HIV virus would help to push the rate of increase upward.

Besides the generally increasing industrialization and pollution, in the 1950s there were sudden increases in our exposure to several powerfully immunosuppressive factors. Radioactive fallout (especially strontium 90, which concentrated its damage near the bone marrow), medical X-rays, dioxins and other chlorinated carbon compounds, insecticides and herbicides, the increased promotion of the use of liquid vegetable oils as food, and the use of lead as a gasoline additive, had all become important immunosuppressive factors by 1960. The relative importance of these varied with the person's age, vocation, customary diet, social class, etc. For example, rich people were more likely to have prenatal X-rays, and poor people were more likely to have lindane applied to their skin to kill lice.

A low level of the hormone DHEA is associated with premature death from various causes, including cancer, heart disease, and AIDS. DHEA is one of the youth-associated, energy-promoting, anesthetic steroids which I have described as essential to our natural resistance. (For example, in "Natural Immunity and Viral Infections," *Ray Peat's Newsletter* #49, July, 1986, I said "Pregnenolone, progesterone, DHEA, and pregnanediol are all good candidates as anti-viral drugs, but etiocholanolone - which also produces fever - is the most interesting of the group.") In general, the things that lower vitality and immunity interfere with our ability to produce the protective steroids.

Those hormones are made from cholesterol, and both low and high concentrations of blood cholesterol are associated with immune defects. Most of the people I have talked to who have multiple serious allergies have very low cholesterol levels, and hypothyroid people who are very susceptible to infections usually have high cholesterol, and in both situations there isn't

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adequate production of hormones from cholesterol.

Often, the idea of "auto-immune disease" serves as an excuse for the use of immunosuppressive treatments, such as glucocorticoids or methotrexate, so I usually avoid the word and the concept. Antibodies against specific tissues are probably part of a normal process to take care of damaged cells. For example, simply twisting a piece of cartilage makes it antigenic. After talking to many people who had anti-thyroid antibodies which disappeared soon after their thyroids became normal from physiological therapies, I decided that "auto-immune" antibodies were useful to indicate which organ was under stress, but shouldn't be taken as a sign of an "immunological disease." Still, the immune system, like any system, can become ineffective or sick, and it is possible that a sick immune system could make some problems worse. (I have previously used the analogy of an "allergy" to discuss this view of AIDS.)

Morphine has been known to be immunosuppressive for several decades, though this fact has been ignored in prescribing it for cancer patients. (Intravenous ethanol has a protective effect on the immune system, and is as effective as morphine in controlling the pain of cancer.) Morphine's directly suppressive effect on immunity isn't understood, but there is some suspicion that it relates to the stress-induced immunosuppression (loss of natural killer cell function, for example), acting in place of stress-induced endorphins. White blood cells, like nerve cells, have surface "receptors" for morphine, which normally would be acted on by the endorphins. As an abnormal material bound to the cell surface, it probably constitutes a "hapten," something sensed by other white blood cells as foreign. It would be healthy to eliminate such abnormally modified cells, and even possibly to eliminate the cells that contain the natural endorphin molecule. But in a weakened organism, the formation of new cells might lag behind the elimination of modified cells."

Deusberg has said that it seems illogical that a person should get sick, just as he is beginning to produce large numbers of antibodies to the HIV virus, but it wouldn't be illogical if the antibodies were eliminating cells faster than they could be replaced. His point, that only one cell in 100 carrying the virus isn't enough to cause failure of the immune system, is true, other things being normal. But an allergy can be triggered by very small quantities of allergen. In a failing immune system, a few molecules of morphine or a few viral antigens could be enough to trigger a kind of autoimmune/allergic response, which could cause a massive suppression or disorganization of immune function.

But even if such a thing is involved in AIDS - even if the HIV virus is a true cause of AIDS - Duesberg is right in emphasizing that we have to think of immune deficiency in a broader context, of eliminating all the immunosuppressive factors, and understanding the real nature of the immune system.

If antibodies turn out to be part of the problem, we shouldn't think of searching for additional immunosuppressive drugs, because we already know of situations in which antibody production increases while immunity is being impaired, as if in compensation for a weakness in cell-mediated immunity. Increasing the production of the cells that are deficient, and improving their functioning, should be the focus of attention. The increased incidence of septicemia among young adults suggests that phagocytosis was deficient. Since Metchnikoff's time there hasn't been much interest in the phagocytes, but I think that is beginning to change.

Note:

*Folic acid is so important for proliferation and differentiation that I think it's worthwhile to take about 5 mg. daily for a week or two. Vitamin A is important for resistance, but carotene can interfere with retinol. Carotenemia suggests a lack of vitamin B12 or thyroid, and interferes with thyroid and steroid production.

Another thought: if you ate vegetables, whole grains and legumes in the 1960s, your bones are rich in strontium 90. Vigorous osteoclasts are working to get rid of it, by phagocytosis. Warm bones are young bones.

Raymond Peat, Ph.D.
Ray Peat's Newsletter
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becomes slightly irregular. Similar effects are sometimes seen following a severe illness or extremely high fever. While the cells are inhibited irregular brown or white porous decay prone enamel or no enamel at all is formed. At the same time collagen forming cells are also disturbed and irregular joint and bone formation occurs. With 20% of the nation's children living in a fluoridated community already exhibiting this fluorosis, it seems that further investigation of the ever increasing arthritic changes in adults is warranted.

"The damage is permanent and in severe cases the cosmetic restoration is very costly. If only the front 12 teeth are treated, the minimal life expectancy of such treatment, 8 years, makes the lifetime expense extremely high. The average cost of crowning (capping) 12 teeth in my city is approximately $6,000 U.S. In a child of 16, that equates to a lifetime expense of $48,000 in today's dollars to treat this 'cosmetic' problem."

Physicians, dentists, health care practitioners in the U.S. have a responsibility to protect their patients from cancer-causing agents. Therefore, Safe Water Coalition of Washington State urges every responsible physician, dentist and health care practitioner to exercise their authority in this matter by immediately calling on public health officers, and contacting their elected representatives – federal and state – to terminate water fluoridation in the U.S., or at least suspend fluoridation pending peer review of the NTP and Proctor and Gamble studies.

Betty Fowler, Spokesperson
Safe Water Coalition
of Washington State
W. 5615 Lyons Court
Spokane, Washington 99208

Emprise Should Evaluate Conventional *and* Alternative Treatments Comparatively

Editor:

I hope you will be able to engage the Emprise people in a dialogue on the various approaches to cancer therapy. I think some of the people who seem so rabidly opposed to any therapy that deviates from the "standard" therapy of the moment are just misled by the claims that seem to be accepted by "all the respected authorities." Several years ago there was a lot of publicity about the great improvement in the rate of cancer cures in recent decades, but someone pointed out that the death rate from cancer hadn't improved at all. About 20 years ago, Harry Rubin (an honest researcher in cancer-related matters) pointed out that if you aggressively hunt for cancer in any symptom-free 50 year-old person, you are likely to find it, since autopsies show identifiable cancer cells in everyone of that age. If refined techniques of screening for cancer (such as whole-body MRI) are developed, we can theoretically get extremely high "cure" rates without lowering the death rate at all.

Until recently, the American Cancer Society continued to base its propaganda on a weird procedure called "age standardizing on 1940," but they have stopped that. The post-war baby boom made the average population younger for a few decades, but now the birth-control pill is making the average population older. In this situation, the trick of comparing the death rate for childhood cancer in, for example, 1950, to the rate in 1986, would make it appear that childhood cancer was being defeated, just as the 1940 reference made it seem that the rate for old people has been improving.

Even the A.C.S. admits that radiation causes leukemia and other cancers, but they are apparently not interested in the effects of fallout from nuclear bomb tests on the leukemia death rate. Anyone who is sure that childhood cancer is being conquered by chemotherapy should consider Ernest Sternglass's discussion of the effects of radiation exposure on the incidence of miscarriages, congenital hypothyroidism and other birth defects, leukemia, brain cancer, and brain development. Since the 1963 agreement to stop atmospheric testing radiation exposure has been decreasing, and so I would expect a real decrease in the childhood leukemia incidence. If you added a real decrease in incidence to the decreased percentage of children in the population, you could get a nice fat decrease in the deaths-per-100,000-population.

I have read widely in the conventional cancer literature, and I think the research is generally crummy, with a shockingly high proportion of what looks like deliberate distortion. It takes a long time to form a picture of what is going on in a particular area of research, unless you have some clues to begin with. A group like Emprise could do exactly the same thing for conventional therapies that they are doing for alternative therapies. This would make their work more credible.

Many people who were about to submit to a "standard" treatment have asked me for my opinion, and when I tell them they ought to read the research that their doctor feels is decisively in favor of the treatment, many of them decide not to proceed with that treatment. A few times I have given people reference to publications in the hospital library, and their doctors have refused to give them permission to use the library. I'm sure that an extensive and coherent compilation and evaluation of the scientific basis of conventional medicine would wreak at least a little havoc.

Ray Peat
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Eugene, Oregon 97405

Correction Notice

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23 March 1990

RE: HAYHURST, Donald

Dear Dr. Collin:

The above captioned individual contacted our office to verify his enrollment dates through University of California, Los Angeles Extension. With the information that he provided our office, his inclusive dates of attendance are as follows:

02/27/80 through 12/31/81

Any other date verified with our records office, at any earlier time, should be disregarded, hence this is the corrected period of enrollment.

If you have any questions regarding the above, please contact me at (213) 825-0167.

Sincerely,

LA Surgent

LeighAnn Surgent
Records Assistant
UCLA Extension

/las

cc: Donald Hayhurst

from Ray Peat's Newsletter (Feb, 1986)

Inhibition and Vitality. In the Achilles reflex test, slow relaxation of the calf muscle is used to demonstrate the low metabolism of hypothyroidism. In the high energy person, relaxation is instantaneous. This is a general principle for the brain and other tissues: the high energy state is relaxed. Epilepsy is an example of a very low energy state of brain cells. Insomnia is a low energy state, and is usually cured by the right dose of thyroid hormone, with adequate glucose and other nutrients. Insomnia is extremely common in aging people, and is the main problem at menopause. Inflammation is another example of a low energy state. Specific patterns of symptoms can be produced by reflexes, and these reflexes can be stuck in place by an energy deficiency. Focussed activity and an alert readiness to respond are prevented by a low energy state, which can cause us to get stuck in inappropriate activity, ranging from worry to "auto-immune" conditions. The inhibited state of nerves has not been a popular field for research in our culture, but the knowledge gradually accumulates. Another type of inhibition has been described recently, in "Acetylcholine hyperpolarizes central neurones by acting on an M_2 muscarinic receptor," by Egan and North, in *Nature 319*, 405-407, January 30, 1986.

Burton. Last year the Center for Disease Control tested some of Dr. Burton's immuno-augmentative therapeutic material, and found that 50% of it was contaminated with AIDS virus (at least the antibodies), and that all of it tested positive for hepatitis. Since he had been getting all of his blood from the U.S., from commercial sources, this sounded suspicious. In the 1960s he was highly respected. The year he got in trouble, 1975, was the year the cancer establishment decided to follow his leads in immunotherapy. Dr. Coley's toxins were removed from the "quack remedy" list. Last year, when Burton's institution was closed down because of the incredibly high rate of AIDS contamination, was the year that the biggest institutional researchers began their promotion of the tumor necrosis factor—which Burton discovered. Burton used a variety of blood derived materials, but purification will be necessary before a drug company can control it satisfactorily. If the stuff doesn't kill people, along with the cancer, it also has great financial potential as a weight-loss drug. I have been trying to learn his side of the contamination story, so I recently tried calling his 800 number, but I was too late, and the woman who answered said she had no knowledge of his organization, she just worked for the U.S. Army. If you know his address, please let me know.

Black Body Radiation. A red hot object radiates lower energy, longer waves than a very hot star does, and a warm person radiates slightly longer, lower energy waves than does the red hot object. The peak of our radiant emission is long infra-red, and we are fairly transparent to that wave-length, so we are black body emitters, regardless of our skin color. It has been calculated that 70% of our metabolic energy is spent as radiation. If we are surrounded by large amounts of mass at our own temperature, we will absorb about as much as we lose. Several years ago, lab rats were kept at a constant temperature, with constant 12 hour light periods, were found to experience a decline in thyroid function during the winter. I had noticed a similar effect in hamsters, atrophy of the thymus gland in the late autumn. Since long-wave infra-red and longer wavelength microwaves can penetrate walls to some extent, it could be that the absence of that kind of radiation during the winter is the stressor which causes these changes, and the mitochondrial damage which occurs in the winter. It could be that some of the therapeutic effects of natural hot springs are caused by gently appropriate radiation from the large masses of hot earth in the vicinity. I think these longer waves might also have an anti-free radical effect, possibly by acting on solvated electrons.

Forests. In the early 1950s I went back to a stream I had seen a couple of years earlier, in southern Oregon; it was one of the most beautiful places I had seen. On my second visit, it had been absolutely destroyed by loggers, who had bulldozed earth, broken logs, and rocks into it. It was just one of the many small streams where fish used to spawn, that have now been destroyed by loggers. A forester has said that much of southern Oregon will never be able to grow forests again, because the soil was eroded after the trees were cut.

A recent news item mentioned that the Atacama desert in Chile also used to be a humid coastal forest, and that it was destroyed by loggers. Another news item mentioned that removal of trees from the Mexican hill where the Monarch butterflies migrate for the winter, was lowering the humidity to such an extent that the butterflies might not be able to survive, even though their own trees are not removed. This effect of trees on humidity is very important, but it is usually overlooked. The concept of "desertification is widely accepted when it is applied to another continent (the Sudan, for example), but not when it might relate to a local resource which supports the area's biggest industry.

When I first went to Mexico in 1955, I was shocked by the huge gullies that were being eroded through the dark brown soil of the hilly grass-covered expanses in the western part of the State of Mexico. In later years those sharp cuts through the muddy earth had disappeared, and a smooth contour had returned, but the remaining soil was pale and rocky, and barely supported grass. A few years ago I learned that this region had been covered by the same dense pine forests which still exist in some parts of the state, but that a foreign company had removed the forests early in this century. A place there is still called El Yukon.

Now that most of the forests, from the California redwoods into Washington, have been destroyed, the center of the logging industry has moved north into Canada. Foresters describe the logging technique used there as "extraction," and say it won't be long until their forests are depleted, so that maybe Oregon's forests will regain their competitive position. Canada's Yukon might someday resemble El Yukon in Mexico. When a region doesn't go directly from a conifer forest to a desert, it may be replaced by deciduous shrubs and trees. The ultimate outcome of this replacement is unknown, but I think we are already seeing some of the effects. Conifers are good at conserving water: they transpire sparingly in the hot, normally dry summers of the Pacific coast region, but they do transpire a little in the winter. Humid air is lighter than dry air: a massive forest allows ocean air to circulate over the land in winter, yet a conifer forest does not extravagantly increase the humidity in the summer. A deciduous forest, leafless in winter, allows dense cold dry air to accumulate, which diverts the humid ocean air. In the summer, however, their intense transpiration tends to intensify the entry of air from the ocean, with the result that rainfall tends to become seasonally reversed, and some of the winter moisture is dumped further south. People who defend the lumber industry's practices say that the forces controlling weather are too big to be influenced by human activity, but several studies show otherwise. For example, the absence of vegetation in the city of St. Louis causes such intense summer heating and updrafts that corn production has doubled in an area down-wind, from the resulting increase in the summer rainfall.

Caffeine. A study in Israel, where there has been no publicity about a connection between caffeine and breast disease, found that using caffeine or avoiding it had no effect on breast disease. A letter in JAMA (Feb. 14, 1986, vol. 255(6), page 748) says "most reports show no significant correlation between fibro-cystic disease and methylxanthine intake." He says "there was considerable evidence to suggest that caffeine has antineoplastic effects." He also says that "caffeine intake had a significant association with tumor differentiation .... Since poor tumor differentiation is linked with decreased survival, the question is raised whether caffeine may have had a beneficial effect in these women." All of the experiments in cell culture similarly suggest that caffeine might be beneficial.

Cystic Fibrosis. Several years ago a "mutation" was discovered in a regional primate center which was said to be equivalent to human cystic fibrosis. A researcher there couldn't believe that an identical mutation could have appeared at the same time in five or six apes; he believed that their symptoms resulted from poisoning from the large amounts of unsaturated vegetable oil they were being fed. He was fired immediately; the new "gene" would have brought in large amounts of research money. A recent study of young adults with cystic fibrosis found that they had low serum levels of both selenium and vitamin E. This seems to support the ex-scientist's theory. (*Lancet* 2:862-863, 1985.)

Food Radiation. As sulfite is removed from foods, pressure will increase for wider use of radiation to extend shelf life of many foods. Proponents are saying that some public education will be necessary, because radiation causes instantaneous changes which modify flavor and texture of foods, making people think they are not fresh; people must be informed, they say, to realize that the spoiled taste and consistency actually means greater freshness, since their shelf life has been extended by many weeks. Radiation, of course, stimulates oxidation of fats, among other changes (called "unique radiolytic products," URP), and rancid fat is toxic and carcinogenic. ■

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Aging Ovaries: Not the Eggs

by Ray Peat, Ph.D.
Ray Peat's Newsletter

A few months ago public television ran a long program on the menopause, in which a rather glamorous woman physician said some shockingly ignorant things about the ovaries and menopause. I went to some book shops, to see what she might have been reading, or hearing in conversations.

One writer thought it would be nice to change the name of the menopause to "the pause." Another said it is too judgmental to say that the ovaries "fail" at menopause, and that they are really just maturing. Those concerns with terminological politeness remind me of Woody Allen's remark about death – that it is nature's way of telling us to slow down.

All of these current paperback books about menopause subscribe to the same doctrine about reproductive aging. Uniformity of opinion creates an environment in which publishers who want to sell a lot of books feel that they have to publish things that don't disturb the reading public. Books about menopause become books about an *attitude* toward menopause.

Even people who like to say that the ovaries "don't fail" at menopause describe a theory in which menopause and its consequences are the result of the disappearance of eggs from the ovary. That theory is so simple it can be described in three short sentences, none of which is true: (1) ovary runs out of eggs; (2) ovulation produces hormones, so you can tell when ovulation stops because the ovaries stop producing hormones; (3) menstruation stops because ovulation has stopped. Those principles are surrounded by various corollaries. "Estrogen is the female hormone." "Estrogen deficiency accelerates aging." "Treatment with estrogen makes you more feminine." "Progesterone deficiency is the result of anovulatory cycles."

Many experimenters have demonstrated that old animals that have become infertile keep producing eggs. Several experimenters (e.g., R. R. Maurer and R. H. Foote,[1] 1971, "Maternal ageing and embryonic mortality in the rabbit," *J. Reprod. Fert.* 25, 329-341) have removed eggs from the ovaries of old animals, and transplanted the fertilized eggs into young animals, where the embryos were able to implant and develop normally.

I found that old animals had too little oxygen in their uterus to keep the embryo alive at the time it would normally be ready to implant itself in the uterus. Giving estrogen to a young animal causes a similar lack of oxygen in the uterus, and prevents implantation of the embryo.

At the time old animals would normally have become infertile, they remain fertile if they are given a supplement of vitamin E and progesterone.

It is now established that aging animals, at the time they become infertile, are deficient in progesterone, but still produce estrogen. Even in young individuals, when stress occurs around the time of ovulation, interference with progesterone production will prevent implantation. If progesterone becomes deficient after the embryo has become implanted, miscarriage occurs.

Estrogen, acting alone or with insufficient progesterone, causes spasms in the spiral arteries that provide oxygen and nutrients to the endometrium. This seems to be the basis for menstruation, and is also believed to be a factor in miscarriage.

About 30 years ago, researchers began to understand that reproductive aging was not caused by the lack of eggs, and the aged uterus was able to support pregnancy if it had the right hormonal support. Interest turned to the brain cells in the hypothalamus which regulate the pituitary. G. H. Zeilmaker ("Effects of prolonged feeding of an ovulation inhibitor (Lyndiol) on aging of the hypothalamic-ovarian axis and pituitary gland tumorigenesis in rats," *J. Endocrin* 43, xxi, 1969)[2] was one of the first to suggest that ovarian hormones caused the brain to age. More recently, P.M. Wise[3,4] has clearly demonstrated that estrogen exhausts the cells which inhibit the pituitary gonadotropins, with the result that even abnormally high levels of estrogen are unable to turn off the pituitary secretion of the hormones that drive the ovary. Estrogen itself can impair the ovary's ability to produce progesterone, but the continuously high secretion of gonadotropins disturbs the ovary, the adrenals, and (according to recent observations) even the uterus.

Stress, especially when augmented by estrogen, leads to injury, exhaustion, and aging. The uterus and ovaries participate in the response to stress, but (as Zeilmaker and Wise have shown) the brain proves to be more directly involved in menopause than the ovaries or uterus. Coordination turns out to be crucial for complex processes such as ovulation, fertilization, and implantation. The destruction of the nerve cells that regulate the pituitary makes coordination impossible.

The issue of "running out of eggs" can be settled simply by demonstrating the presence of viable eggs at the time reproductive ability has ended. In the 1940s, menopause was "explained" in terms of an estrogen deficiency, without a basis in fact, and now an "egg deficiency" is combined with the "estrogen deficiency," compounding the confusion. Facts aren't everything in science;* it is necessary to look at the context from which these ideas develop.

Two of America's most productive researchers in reproductive physiology, Edgar Allen and Herbert M. Evans, made observations that they believed showed that the germinal epithelium of the ovary goes through a cycle of cell proliferation that produces a new generation of oocytes during each menstrual cycle. It is recognized that new egg cells appear in the ovaries of adult prosimian primates, and at puberty in cats and pigs. Observations of newly developed egg cells have been reported in some other species. But the dominant view prefers to see the number of egg cells declining from birth, or earlier, with absolutely no new egg cells being formed later.

During gestation and infancy, the gonadotropins are very high. These hormones decline during childhood, during the time that the number of egg cells is so visibly declining. The high level of the gonadotropins during infancy hasn't been explained, but it is reasonable to suppose that it has something to do with the development of the ovaries, since a "developmental"

function can be demonstrated for the gonadotropins in the ovaries and testes of older animals.

The number of brain cells peaks a few months before birth, just as the number of egg cells does. Many people have argued that this somehow means that brain cells are incapable of dividing after infancy, though there is no factual basis for making that argument, and in fact adult brain cells are now known to be able to divide. (That is true of heart cells, too.)

In a variety of tissues, it can be shown that the presence of mature cells inhibits the division of other cells. If part of the liver is removed, the remaining cells divide to replace the lost tissue. If the skin is cut, cells divide to help fill in the defect. If there is an adequate number of egg cells, this principle suggests that there is no need to produce more. There is a treatment for polycystic ovaries called "wedge resection." This can reduce the production of masculinizing hormones. By analogy with other tissues, it seems likely that the removal of a mass of malfunctioning tissue leads to the growth and development of new cells which function the way a new ovary would. Regeneration seems to be a capacity of every tissue, given the right environment. If the ovary were studied after such treatment, I suspect that "new eggs" would be found. (But even in the seemingly simple process of healing a wound in the skin, there is still disagreement as to the relative contribution made by local cell division, and the invasion of the region by structural cells from elsewhere in the body. The appearance of a cell can be misleading; histology is often a matter of making educated guesses. For example, white blood cells can look like epithelial cells.)

Although the question of whether all the woman's eggs are in existence at or before birth doesn't logically have anything to do with the other question, whether there are still eggs in the ovary at menopause, there is a reason that people connect them. This has to do with the idea of a "germ line" as distinct from the "somatic cells." The eggs are "from the germ line," all the rest of the body (and much of the ovary) is a different sort of stuff. The "germ line" has the special property of immortality and it is "isolated" and independent. The body is susceptible to being modified by the environment, and is mortal. These are the traditional formulations of the idea, and the people who learn their orientation from textbooks are not necessarily conscious of how the ideas fit together. For biologists of my professors' generation, these ideas seemed to be a sacred core of biology, but with their death, maybe biology can be liberated.

August Weismann, working at the end of the last century and the beginning of the 20th century, created the basic ideology of genetics, to combat the idea of the inheritance of acquired characteristics, which had been supported by Darwin and others. He argued that the hereditary substance, or germ plasm, was derived only from preexisting germ plasm, and couldn't be formed anew, or modified by the environment. It created every part of the perishable body, by a process in which traits were segregated, so that the germ plasm contained the full complement of hereditary material, and each part of the body contained only the limited fraction needed for its characteristics. Thus, the body was inferior created material, while the germ line was the immortal creative stuff. Since the body adapts in response to the environment, it had seemed that these changes would be passed on to descendants, until Weismann's argument showed that it was only the perishable, dead-end body lacking the hereditary principle which was adapting. The germ line was somehow isolated from the body and from the environment.

Weismann's theoretical germ line became identified with the chromosomes and the genes. His theory was shown to be simply wrong, in that each type of cell in the body contains a full complement of chromosomes and genetic information. Although his facts were wrong, his ideology became deeply embedded in the culture of genetics. To keep the idea that the "germ line" is somehow something distinct from the body required a special effort, once the chromosomes were seen to be identical in every part of the body. Weismann's whole point in his "germ line" idea was to show an absolute distinction between the body and the hereditary substance. If his ideology that had been built to deny the inheritance of acquired characteristics were to be saved, the *isolated* germ line would have to be found elsewhere than in the chromosomes.

The idea of "germ line (or *Keimbahn*) determinants" now took over, and was believed to be something in a certain spot in the egg. As the egg divided, into cells that look very much like each other, the cells which came from *that* part of the egg represented the germ line. As the embryo developed, the region that seemed to be traceable back to that part of the egg, represented the germ line. As the gonad began to grow, cells from the region representing the germ line were thought to travel over and invade the gonad, where they multiplied into vast numbers, but always remained the same isolated strain of germ cells with their "separate" history that could be traced back to the determinants in the special place in the egg. During the early days of embryonic development, these immigrant cells looked exactly like their neighbors which were somatic cell sprouts from the embryonic kidney region.

If it weren't for the ideology of absolute isolation of the hereditary substance, an embryologist might have suggested that cells or material of one part of the embryo *induced* a specialized, differentiated state in some cells that happened to be suitably located. If the cells derived from that certain part of the egg didn't carry unique genetic material – and they didn't – then what they carried with them was an incipient state of differentiation. Why the big deal about that particular history of differentiation? It was because the ideology that motivated Weismann was still active, and its purpose was to argue that only the "gene" was the creative productive source, and that the body – the "somatic cells" – was the passive product, whose adaptations meant nothing in the long run. This has been called the "central dogma" of genetics, that information flows only from the gene to the cell, and not back from the cell to the gene. That ideology forced geneticists to deny the existence of RNA viruses (including retroviruses such as the HIV-"AIDS" virus), and is still active in blocking research on the prion or scrapie virus, which is a protein. To say it bluntly, many highly respected biologists acted stupidly because they

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Aging Ovaries

blindly believed in a false ideology.

Incidentally, this ideology was always impossible for horticulturists to accept, since they were in the habit of grafting (cloning) vegetative (somatic) parts of plants, which would then produce flowers and fruits. For them, the "germ" was often a product of the "body." Luther Burbank's work was consistently ridiculed by the academic biologists, who believed his achievements were impossible, that is, fraudulent. Many of Burbank's perceptions have been supported by recent evidence, but they couldn't be accepted by people whose ideology of the germ line/somatic distinction seemed to be contradicted by his work.

Another problem with the doctrine of the germ line was revealed when embryologists separated the embryo at a very early stage into two groups of cells, and found that each was able to grow into a complete animal. The idea of the germ line predicts that one member of the pair of twins could get the ability to reproduce while the other would be sterile. Some important ideas can survive their disproof.

It is exactly the same academic ideology of the priority of the germ line which blames the whole complex process of reproductive aging on the mechanical process of an "ovary running out of eggs." The ovary doesn't run out of eggs, and running out of eggs would have no great consequences if it did happen, because the main events in ovulation are produced by cells other than the eggs. But the ideology says that the "germ line" controls everything, and the eggs are the germ line. In other words, genes control the organism, and eggs control the woman.

I think it will be instructive to consider the three steroid secreting glands – ovaries, testes, and adrenals – together, to see what they might have in common. In the testes, it is generally believed that pituitary gonadotropins regulate steroid synthesis and gametogenesis. In the ovaries, the gonadotropins also regulate the production of steroids, and – to some extent – the production of eggs, if not the whole gametogenic process. In the adrenal, ACTH governs the production of cortisol and sex steroids, and the transformation of the glomerulosa cell type into the other types, which secrete those hormones.

The outer layer of cells in the adrenals can form the other two cell types, and since stress ACTH converts them to the other types, new ones must be formed. If the inner layers are removed, the whole adrenal cortex can regenerate from the outer layer Obviously, if stress causes cells to multiply and differentiate, cells are disappearing from the inner layers.

When I was in graduate school, immunologists were aware that new cells were continually appearing in the thymus gland, but the gland didn't get bigger, and there was no visible trace of dying cells. At that time, it was considered a major puzzle, but gradually it came to be understood that a special kind of cell dissolution (called apoptosis) was occurring that accounted for the missing cells.

In the testes, apoptosis or cell-dissolution is always occurring, even though sperm cells are being produced and leaving the organ.

In the ovary, "waves" of egg cell degeneration are constantly taking place in young women. Radioactive labelling that has been used to argue that egg cells aren't being replaced seem to show that there is continual cell division in all the other ovarian cells. Interestingly, those researchers didn't seem to be interested in this apparent regeneration of the other parts of the ovary.

Apoptosis always seems to be part of a shaping process of the organ in which it occurs. Regeneration provides new cells, apoptosis recycles the substance of a certain fraction of the tissue's cells. We are just starting to notice that various hormones inhibit or promote apoptosis, and so participate in the "shaping" of the organism. In many systems, it seems that the need for a cell type or function calls it into existence, while idleness makes a cell susceptible to dissolution.

I have been referring to the "pituitary gonadotropins," and deliberately avoided referring to them as LH – luteinizing hormone – and FSH – follicle stimulating hormone – because their names reflect a theory of what they do. In some textbook descriptions of testicular function, for example, it has been said that LH produces testosterone, and that negative feedback from testosterone suppresses LH, while FSH governs the formation of sperms. That description is completely worthless, and probably was largely built up by analogy with their supposedly neatly divided functions in the ovary, reflected in their names. These gonadotropins participate in the development, maintenance, and functioning of the ovaries, and their effects depend on their timing, their balance with each other and with the steroids produced by the ovaries in response to their stimulation, and their actions are modified by many other factors, ovarian, nervous, pituitary, uterine, and immunological. During youth, the system functions in a coordinated way, with ovulation as a consequence. During aging, the crucial changes appear to be a decreased ability of the ovary and the brain to produce progesterone. Thyroid hormone, cholesterol, vitamin A and efficient cellular respiration are essential factors for synthesizing progesterone. Accumulated iron, unopposed estrogen, and impaired use of cholesterol and oxygen are factors known to contribute to the widespread and variable damage to the system of coordination.

Two things can cause the pituitary to secrete excessive amounts of the gonadotropins: A deficiency of the steroids, and damage to the steroid sensing nerves that regulate the pituitary. When an ovary is moved (transplanted into the spleen) so that its hormones are destroyed before getting to the brain, there is hypersecretion of gonadotropic hormone,[5,6,7] and tumors develop in the ovary. The interpretation, that hypersecretion causes the tumors, is supported by other observations, e.g., that removal of one ovary increases the chance of developing a cancer in the other ovary and that prolonged use of estrogen (known to create the conditions for later hypersecretion of gonadotropin)[3,4] increases the risk of ovarian cancer after menopause.[9]

Psychologists have noticed that naming an object according to a certain function often limits the way people will be able to use it. This happens in science. If we know one function of a substance, and name it for that function, we will find it harder to think of its other possible roles. Hans Selye argued that

steroids, for example, should be named according to their place of origin, rather than by a single aspect of their function. I think this applies even to the phrases "male hormone" and "female hormone": it's better to think of them in terms of their origin, and not to count on them to promote femininity or masculinity.

A note about "the female hormone." In the absence of the testicular or "male" hormones, animals differentiate as females.

Progesterone is an anti-androgen, and blocks testosterone's effects. When testosterone is given to newborn or very young rats, it sets up a male pattern of hormone development, but if progesterone is given at the same time, that doesn't happen. Progesterone prevents the differentiation away from the basic female path into the male specialization. Later in life, a deficiency of progesterone in a woman can again lead to masculinization of some features, such as musculature and facial or body hair. When progesterone is given to men in large doses, it blocks various typically male processes, such as growth of whiskers. In the brain, it has a protective function in both sexes.

Estrogen promotes cell division, and is involved in essentially every tissue, in both males and females. If it is to be called a "female hormone," maybe it also has to be called "a male hormone." It does have to be present for breast development, though it is just one of many factors. In this instance, it is contributing to feminization. In other instances, it seems to contribute to virilization.

At menopause, estrogen excess can promote the production of androgens, in the absence of progesterone, which tends to defeminize the woman. This is often a result of stress, and sometimes is a consequence of hypothyroidism. In situations of this sort, estrogen is seen not to be a feminizing hormone; it is unable to neutralize the male hormones the body produces in response to the estrogen excess.

Footnote*

Since the 1930s, estrogen's toxic potential has become very clear. However, the estrogen industry doesn't want people to understand that estrogen is a shock hormone with pro-aging effects. Histamine mimics estrogen's effects on the uterus, and antihistamines block estrogen's effects (Szego, 1965, Szego and Davis, 1967). Estrogen mimics the shock reaction. Stress, exercise, and toxins cause a rapid increase in estrogen. Males often have as much estrogen as females, especially when they are tired or sick. Estrogen increases the brain's susceptibility to epileptic seizures, and recent research shows that it (and cortisol) promote the effects of the "excitotoxins," which are increasingly implicated in degenerative brain diseases.

Currently, estrogen marketing emphasizes appearance and the danger of osteoporosis. Evidence occasionally turns up implicating estrogen in thinning of the skin and bones.[10]

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More Letters

human mind and art of living on behalf of the whole human race. We must undertake "the cartography of inner space" untouched by verbalization, and we must establish "inner space labs."[21] When this is deeply realized by the scientific community, only then there will be universal peace and freedom. Actualization of scientific responsibility by the scientists themselves can save us from annihilation, to heal our diseased mind-brain equipment and to heal our planet. Scientific responsibility is the new approach to public health. This ensures "Health for All - All for Health."

It is the primary concern (responsibility) of the UNESCO, the "Universal Movement for Scientific Responsibility," to make this discovery available at the door step of every scientist on the globe. It is of paramount importance that the deeper truths are shared through dialogues and workshops so that there is deeper awareness of "the responsibility of science with regard to the future of humanity, of ensuring that our children's lives will not only be preserved but enriched in peace," in the words of Jean Dausset.[22] The destiny of humanity is hinged on scientific responsibility. We shall survive only if we can show (responsibility) that we deserve to survive. The one truth that a scientist must never forget is that he is responsible for the future of humanity, for the survival of the species.

Kanwaljit
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Education Against Knowledge

There has to be a way to measure the quality and efficiency of a clinic just as there are ways to measure the same characteristics in a baseball pitcher.
Former Surg. Gen. C.E. Koop

Editor:

Years ago, I was told by our state Superintendent of Public Instruction that "what students know has nothing to do with education." Since then I have occasionally wondered how many other people with responsibility for education have such a clear awareness of their social function. Many teachers and professors, who emphatically claim that education has something to do with knowledge, nevertheless will claim that there is no objective way to measure knowledge. Many of these teachers will base their students' grades on examinations, yet it is rare for a school or college to allow a student to take those same exams for full credit without enrolling in the course. Several professions require an examination to qualify for a license to practice, yet will administer the test only to people who have the appropriate degrees, as if the examination (which excludes a fair number of degree-holding applicants) were unable to exclude those with inadequate knowledge.

The National Endowment for the Humanities has done another study, this time showing that U.S. college seniors generally don't know very much. In their earlier study, they found that the average young person in the U.S. knew less about the world than people of the same age in Mexico, Italy, and all the other nations studied. I suppose this country spends at least 50 times as much on "education" as Mexico does. Dr. Koop has pointed out that "health care" in the U.S. is deteriorating, at the same time that its cost is increasing. Just as he proposes that medicine should adopt the serious and objective concern for performance that exists in baseball, I would propose the same for education.

The fear of objectivity in education and in the professions has to do with power. When a professor has secret criteria, his judgment can't be challenged. If his assumptions are unfounded, a student could embarrass him by examining them. But, in a system which requires an accumulation of course-credits, good students quickly learn what is expected of them, and after a few years of learning not to question the assumptions of their "discipline," they are ready to become like their teacher.

Listening to an expert talk about a subject is often a good way to learn, but having your understanding judged by that same expert is very likely to inhibit a spirit of objective inquiry. Separating evaluation from instruction can make a tremendous difference in education. Students and teachers can disagree, and still have a sense of working together. Venerable dogmas and stylish trends can remain in the curriculum, but their mystique is likely to evaporate. Even textbooks are likely to change, because they are now designed to serve the teachers (who select them) rather than the students who use them. Whether the subject is music, or math, or language, or physics, textbooks are likely to be instruments for maintaining a mystique, rather than for directly communicating an understanding of the subject. Vague or fragmentary definitions of terms and symbols often make the subject seem more mysterious than it is.

I have seen teachers present in a day the material that they would normally teach in a semester or two, and it seemed that their students grasped the subject as a whole more clearly than the conventional students who attended dozens of lectures. This was in the early 1960s, at Blake College. This school has been described as a prototype for the experimental college movement of the 1960s, but my intention in creating it was to demonstrate what can happen when students are not required to conform to the cultishly departmentalized attitudes toward knowledge which dominate most schools and universities. Simply by letting the students know that professionalism was not sacred, they were allowed to see how easy it is to master the information which is normally so laboriously and pompously inculcated.

In a miniature way, my composition class at Montana State (1965-66) demonstrated the same process. The department "required" each instructor of freshman composition to grade according to department rules, subtracting so many points for misuse of a comma, or for using the wrong part of speech, or misspelling, etc., with the result that 50% of the students failed the course. A few weeks into winter quarter, I decided that the procedure was just too pointless and degrading, for both students and teachers, and I told my classes that I was going to ignore their grammar and spelling and punctuation when I decided on grades for their papers (though I still pointed out the conventional errors), but that I was going to grade on the content of what they said. If they communicated something of interest, they would get a good grade, but if they kept writing on the level of a grade-school child (which they did in an effort to keep the mechanics of writing simple, hoping to minimize errors) I would give them an F. They immediately started to write more interestingly and more complexly, and the errors in grammar dropped sharply, so that nearly all of them were passing even by the stupid departmental requirements. That spring, the university solicited grant applications for research projects to improve education, so I submitted a description of my class, with before-and-after examples of the student's writing, to demonstrate the dramatic improvmeent. Only one other person, out of the 40 teachers in the department, would talk about the idea of writing for content; I'm sure that the department chairman didn't forward my proposal to the committee that had solicited research proposals, since so many of the old-timers in the department were committed to the idea that the department's "standards" would be lowered if they didn't fail half of the freshmen. (Incidentally, the courses were called "Communication 121," etc., so I argued that it was proper to grade the students on the basis of communication, rather than form). Since then, I have heard many people justify various "educational" ordeals, by saying "that would be like a child trying to learn to speak before learning the alphabet," or something to that effect. Their examples usually make exactly the point they oppose; for example, it would be a seriously distorted child who learned the alphabet before learning to speak. And much of our educational system, at various levels, is devoted to just that kind of distortion.

Unless the dogmatic power of "the authorities" is replaced by some objective standards of knowledge and skill, public knowledge will continue to deteriorate. Our interactions with the environment, with each other, and with other nations will continue to deteriorate. Public health and the standard of living will deteriorate, unless knowledge is treated with the same seriousness as the skill of athletes.

Ray Peat
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More Letters

16 Million Americans Sensitive to Pesticides

Editor:

About 5 million Americans are highly allergic to pesticides and risk severe immune reactions ranging from watery eyes and itchy skin to shock and death when they are exposed to these chemicals, reports Russell Jaffe, M.D., Ph.D., principal scientist at Serammune Physicians Lab, a biotechnology laboratory in Reston, Virginia. Another 11 million have moderate reactions to pesticides ranging from tearing and dripping noses to hives and muscle and joint pain.

This is the first study that makes an accurate determination of the body's immune system response to pesticides - a class of chemicals called biocides used to kill life. In a five year period, the study measured responses of more than 8,000 patients to the three major classes of pesticides - carbamates, organophosphates, and halogenated compounds.

"Our research is the first to clearly link pesticides with immune recognition responses," says Dr. Jaffe. "It is no longer a matter of guess work. Now we can determine for an individual their sensitivity to pesticides." Dr. Jaffe's study data are derived from the ELISA/ACT test, a state-of-the-art evaluation tool of immune system reactions to 235 foods, pesticides and environmental chemicals. This is the first procedure to fully diagnose immune responses - providing physicians an *immunologic finger print.*

In susceptible people even low levels of these pesticides can cause major problems such as asthma, bronchitis, eczema, and migraine. The report estimates that about 500,000 people have these types of responses.

A finding of the study is that more than 16 million people show impaired immune function due to the effects of these pesticides - increasing susceptibility to chronic viral and bacterial infection and decreasing the body's ability to repair itself.

Chronically impaired immune function greatly increases the risk of cancer and heart disease. Future prospective studies are needed to determine the exact nature of this risk.

In study after study, the American public has shown increasing concern about the safety of pesticides in our environment,

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I now have a fulfillment of what I have been wanting to do for some time, and that is to operate a self-help information service, hold self-help seminars on magnetic therapy and engage in research in medical magnetics. I supervise some patients undergoing diagnosis and treatment at American Biologics-Mexico in Tijuana, Mexico. American Biologics-Mexico is an excellent research institution where I can reach my research goals.

I have decided it doesn't pay to give credit adjustments to patients. I found that I had credited an excess of $300,000 and then one of these complained to the medical license board because she did not want to pay her bill. I wonder if we are entering a new day in which insurance companies are going to complain to medical license boards because they do not want to pay for a particular service. I also wonder if doctors now are going to be complaining when a patient leaves them and goes to another doctor, who does more than usual and customary in order to help his patients. I have enjoyed the practice of medicine and part of my joy has been because I have sought out those extra ways to help my patients. My allergy work was guided by a board certified allergist. I have worked closely with biochemists for years. The addition of biophysics to my practice has been on a high scientific level. It seems quite evident, however, that a physician can spend a lot of money just because he is different and just because he wants to help his patients who have not been helped by what the average physician provides.

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Biological Balance and Addictions

Editor:

A good salesman knows how to get on to waves of rising enthusiasm. Intuitively, politicians, cult leaders, and scientists use the same process. The quick rewards of joining a rising tide reinforce the conformists' efforts, and thought needn't go much beyond "this must be true, because it works for me."

In the early 1950's, David Reisman discussed the idea of counter-cyclic activity in economics and culture, as an error-balancing technique. One of the simplest ways to evaluate the meaning of a cyclic process is to see what happens if it is damped or opposed, and to compare these results with an alternative amplification or reinforcement. The technique is useful biologically, as well as socially: pharmacologists have used the method for centuries, and theories of medicine are based on either damping or intensifying the wave-like processes.

Withdrawal from an addictive substance involves a physiological swing to a kind of "opposite pole," or nadir to the zenith of the drug's action. As no drug has just one effect, the deformation of physiology remaining when the drug is removed will not be a simple matter of a single "receptor" molecule. Physiology compensates continuously to maintain balanced functioning in the presence of a great variety of drug-like substances in our diet. When the diet is changed suddenly, eliminating alcohol or caffeine or other biologically active substances, our compensatory counter-cyclic adjustment is revealed.

The return to a physiologically balanced state requires many changes, and these occur at different rates. (The physiology involved in any organismic function consists of overlapping layers, each of which can work alone to some exent, and dysadaptation can affect the different layers - e.g., hormonal and neural - in different ways. And within a given regulatory "layer," such as the autonomic nervous system, there are various kinds of adaptive processes, including adjustment of energy charge, rate of "firing," thresholds, synthesis, and growth.)

It is important to think concretely about the processes in "recompensation" or restoration of balance. Some of the processes we should consider in relation to addiction are: tissue energy charge, metabolic detoxication and elimination, permeability and barrier functions, excitation-inhibition, and poorly compensated stress reactions.

Probably the biggest error in our popular culture of addiction is the idea that craving is triggered by the presence of the substance in the body, and that cleansing the substance from the body will stop the craving. This idea has become quite a cult, with ramifications into theories of obesity, allergy, sexual dependency, and violence.

The common element in these widely promoted cultish systems is a distrust of ➤

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the organism, a body-rejecting attitude that craving is necessarily bad, leading to a blurring of the difference between need and addiction. Cleansing the offending substance from the body to stop the craving suggests that the clean and pure person is without desires. Opposing this other-worldly doctrine is the fact that desires reflect needs, though seldom in a fully rational way. The fact that something makes you feel better, and that you feel worse when you stop using it, shouldn't be taken as evidence of its "addictiveness," but many people feel that way about thyroid hormone, coffee, vitamins, and even the most ordinary foods.

The fact that a taste of chocolate can provoke a wild lust for more chocolate, or that one cigarette renews the addiction, does not mean that the presence of chocolate or nicotine in the blood creates a craving. Rather, it is that an organism in an unstable state perceives the availability of something which promises to partially restore the desired stability. It is obvious that smoking cigarettes is not a good way to achieve the needed stability but this observation can't be generalized to the craving for potato chips, or coffee, or the multitude of other things that people often crave. There is often an easily discovered reason for cravings, and it is more fruitful to suspect that all cravings have a rational basis than to accept the Calvinist or Buddhist idea that desire itself is bad.

The availability of energy is central to our stable functioning, and the need for energy powerfully modifies our functioning. For example, as hunger increases, the brain's interpretive system changes in a way that causes increasingly unfamiliar things to be considered as possible food. The "spreading excitation" that leads to this extended search probably occurs in relation to needs other than hunger, and could lead to experimentation with drugs and to other activities that give some indirect satisfaction. Obsessive and compulsive patterns can sometimes be resolved by assisting the brain's energy metabolism, for example with a supplement of magnesium and thyroid.

But even hunger itself has such ramifications - protein deficiency, salt deficiency, hypoglycemia, elevated adrenalin and cortisol and growth hormone, for example - that a great variety of things could give partial satisfaction. Alcohol can make a powerful and positive contribution to nutrition by sparing protein, and by modifying nutrition-related hormones. (Although some of this work has been published in the *Journal of the American Medical Association*, the stigma attached to alcohol has prevented its adoption as a most useful drug/nutrient, even in terminal cancer patients, where its promotion of immunity could have great value. The abusive stigmatizing of useful substances is an example of unhealthily exaggerated social cycles.)

Behind alcoholism, it is common to find nutritional and endocrine problems, as well as emotional or situational problems. For example, a man who had been unhappy with his work and had struggled with "alcoholism" for 13 years, gave me the impression of someone lacking the basic hormone precursor, pregnenolone. A few minutes after he took 100 mg. of pregnenolone, his depression and anxiety disappeared. Later, he said "that's the feeling I've been trying to get from alcohol, but it never worked." Pregnenolone, more powerfully than alcohol, lowers cortisol while stabilizing other systems. Its highest concentration in the body occurs in the brain, and its level declines sharply with aging: it very likely makes a large contribution to the adaptiveness and sense of well-being which are characteristic of healthy young individuals. In healthy young people or animals, additional pregnenolone has no detectable effect.

"Agitated depression," which is common in old age, is a common symptom of withdrawal from a variety of addictive substances. I suspect that agitated depression, or anxious depression, is a stress syndrome that makes ordinary adaptation difficult. The inability to cope with everyday problems often precedes experimentation with drugs. Low energy and high anxiety can lead a person to use either stimulants or sedatives, or both. Curing the initial problem should make withdrawal from many substances easier, though most of my experience relating to "addiction" has been with "alcoholism."

In 1979, I was thinking about steroid anesthesia, and decided to test whether the newly discovered "opiate receptors" were involved. Naloxone, the anti-opiate, didn't seem to block progesterone anesthesia, but I was still convinced that there was a connection. I think of progesterone as acting at a deeper or more general level, which could allow synergism between opiates and progesterone, without naloxone's blocking the effect of progesterone.*

By chance, a musician who said he had been using heroin and alcohol for 40 years asked if I could help him sober up for an important job that was to begin in a few days. He said he had been continuously drunk for 6 weeks. He brought a quart of beer with him when he came to the house, and since we were having a holiday dinner, he had a chance to keep drinking wine when his beer was finished. At bedtime, I told him about my inconclusive experiments with progesterone, and described the other effects of the material, including its brain-quieting and anti-toxic, anti-stress effects. He took about 100 mg. then (in vitamin E), and took the rest of the bottle to bed with him. Since he had serious cirrhosis of the liver, I explained that he should also take triiodothyronine, since this active form of the thyroid hormone is formed mainly in the liver, and I suggested that his nearly destroyed liver was probably making very little.

He got up around 8 o'clock the next morning, and was smiling and very happy looking. He said he had never had this experience before, of waking up without a hangover after heavy drinking. He had consumed so much of the progesterone that I repeatedly told him to be aware that it could interfere with his sexual function by blocking the effects of testosterone. He stayed alert and sober, and proceeded with his performances. He took about 30 grams of progesterone in vitamin E over the next several months, and said his sexual functioning was perfectly normal. He took 50 mcg. of Cytomel morning and night, and his doctors gave him a few injections of magnesium. His doctors noticed that his liver was getting smaller, and about a year and a half later they said it was normal, without cirrhosis. (Since then other people have noticed similar effects on inflamed and enlarged livers, when taking progesterone with vitamin E and thyroid.)

Both progesterone and triiodothyronine have the function of increasing the tissue's energy supply, and in suitable doses can have a steadying , calming effect. While many people think of thyroid as a kind of stimulant, because it can cure the coma or lethargy of myxedema, this is a very misleading idea. In hypothyroidism, the brain exciting hormones adrenalin, estrogen, and cortisol are usually elevated, and the nerve-muscle relaxant magnesium is low. Normal, deep sleep is rare in a hypothyroid person. The correct dose of triiodothyronine (the active thyroid hormone) with magnesium is a reliable treatment for insomnia, cramps, and anxiety, whether these symptoms are caused by fatigue, or aging, or alcohol withdrawal.

Aging, stress, and heavy consumption of alcohol increase the permeability of the intestine, causing increased absorption of microbial toxins. Laxatives, carrot fiber (not carrot juice), activated charcoal, and a small amount of sodium thiosulfate decrease the formation and absorption of toxins, increasing the organism's adaptive capacity. Belladonna can improve the bowel's function if there are spasms during drug withdrawal.

Camphor, adamantanamine (amantadine, Symmetrel), and "local" anesthetics taken systemically, can help in withdrawal from stimulants. The conventional (200 mg.) dose of camphor and adamantanamine shouldn't be exceeded. (The hormones thyroid, progesterone and pregnenolone alone are sometimes enough.)

Smoking is probably the hardest addiction to break, but careful use of nicotine gum with belladonna (to block some of the circulatory effects of nicotine) can allow a person to avoid the worst toxins of the smoke while overcoming the behavioral habit of handling cigarettes, without having to simultaneously modify the chemical addiction. Caffeine[1] and vitamin A are very protective against cancers, including those induced by smoke. Progesterone and pregnenolone both have anti-toxic (or "catatoxic") effects, though their effects on nicotine craving are slight.

Our society's mystique about drugs makes it hard for people to rely on their own judgment and experience. If they want to try to feel better, aspirin, coffee, tobacco and alcohol are normally the only drugs they have to experiment with. Too many physicians think of "euphoria" as an undesirable side-effect of certain drugs, and are likely either to recommend stoicism, or to mechanically prescribe one of the standard mood altering drugs. Ideally, a physician should view unhappiness and the feeling that life is getting too hard to handle, as a biological problem to be explored in cooperation with the patient. If circumstances are responsible, and can be changed, the biology will take care of itself.

The institutions and cults that have grown up around "treating addiction" are not so different from the cults and institutions (including the pharmaceutical industry) that surround the use of drugs. Rationality and concern for the full range of real needs of people are likely to be ignored when stereotypes and ideologies can be used so profitably.

Dealing with addictions as having (directly or indirectly) to do with real needs can help to remove some of the unnecessary guilt and anxiety associated with addiction. This makes it easier to find out what is really needed to move toward a stable and balanced physiological state. As simple as it is to recognize addiction as a process of biological adaptation, there are many tricks for evaluating and facilitating the process, that can be discussed in more detail later.

Painters and musicians have sometimes said that they use alcohol or other drugs to help them find their "own way." Moving against the tide of the culture is an adaptive effort, and they find some neurological support in drugs. They are right in struggling against the current of imbecile conformity to find some creative truth, but there are better ways to sustain our energy and adaptive capacity. In some cases, good food and social fairness are enough to enliven people so that drugs are not attractive, and in other cases a more specific biochemical/energetic approach is needed.

Notes:

*The systems which respond to valium and atropine are the places that I would want to look for clues to progesterone's effects on addiction.

More Letters

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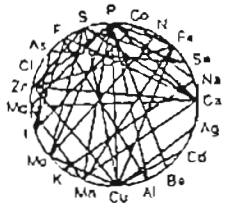

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A Physiological Approach to Ovarian Cancer

Several years ago, George Crile, of the Cleveland Clinic, observed that his clinic had removed only 11 thyroids that year, and that they had done more than 5000 thyroidectomies annually in the 1920s. The reason for the change was that they found that there was rarely any reason to remove the gland; even thyroid cancers of most types could be controlled safely by using a thyroid supplement, to reduce the growth-stimulating action of the pituitary hormone.

Since many physicians still believe that destruction of the thyroid gland, by radiation or surgery, is an appropriate treatment for thyroid disease, it isn't surprising that there is so little attention given to the possibility of physiologically controlling the more aggressive ovarian cancers. The recent report that ovarian cancer is more common among women who have taken gonadotrophins, to promote fertility, will probably bring increasing attention to the physiology of ovarian tumors.

Around menopause, the pituitary gonadotrophins increase. Menopausal estrogen treatment shouldn't be called "estrogen replacement therapy," because the amount given is typically about 15 times higher than occurs in younger women. The reason for the use of such high doses is that the dose is increased until the pituitary gonadotrophins are suppressed. The reason for the menopausal increase in pituitary hormones is that the nerve cells which regulate their secretion have been killed or desensitized by their past exposure to estrogen; it is their reduced sensitivity that requires the very large doses of estrogen to suppress secretion of the gonadotrophic hormones.

Clonidine (normally used for high blood pressure) can be used as a skin patch, to control menopausal flushing; progesterone and DHEA prevent osteoporosis. After those issues have been taken care of, the question of pituitary hyperfunction should be considered, in relation to preventing ovarian cancer. (Combinations of safe substances including progesterone and naloxone can probably be worked out empirically.) A variety of other possibilities exist, including Gonadotrophin Inhibiting Substance, and antagonists to the specific gonadotrophin release hormones. Normalizing the menopausal gonadotrophins would have far-reaching effects, possibly improving the immune response.(1)

For years, it has been known that nuns have a high incidence of ovarian, breast, and endometrial cancer. Women who have children, or who take oral contraceptives that might suppress ovulation, are believed to have a lower incidence of ovarian cancer because of reduced exposure to the gonadotrophins. (Though cancers of liver, breast, and other organs are reported to be more frequent among pill users; prolactinomas seemed to become epidemic after the pill was introduced.)

Normal factors in the physiological control of the ovaries include an interaction between the thyroid and the gonadotrophins; the combination of hypothyroidism and stimulation by gonadotrophins can cause ovarian cysts to develop. Small amounts of estrogen can increase both FSH and LH, and large amounts of progesterone decrease both FSH and LH.(2)

If ovaries are removed from their normal location, and transplanted into the spleen, so that their secretions go directly to the liver where they are inactivated, they produce tumors because they are subject to "hypersecretion of gonadotrophic hormones."(3) Other experiments support the idea that ovarian tumors develop from excess pituitary stimulation. For example, removal of one ovary was essential to produce a tumor in the other ovary even after it had been irradiated.(4) Similarly, no tumors developed in irradiated ovaries transplanted into other mice, irradiated or not, as long as they had their own ovaries, which kept the pituitary functioning normally.(5)

Progesterone and estrogen "receptors" can be demonstrated in some ovarian tumors, and by analogy with breast and uterine tissue, in which progesterone generally retards cell division and estrogen stimulates it, hormones have been investigated as possible therapies for ovarian cancer. Although in vitro studies show that there might be a direct action on the tumor cells,(6) the reports of positive responses in patients treated with progesterone or synthetic progestins(7) are more interesting, since the most logical approach involves normalization of the pituitary gonadotrophins.

If it is true that a "deficiency" of the so-called "essential" fatty acids suppresses gonadotrophin secretion,(8) then a diet lacking those estrogen-promoting(9) substances should be both protective and therapeutic for ovarian cancer (assuming that the results seen with progestin therapy are produced by gonadotrophin inhibition.) If our purpose is to delay the menopausal rise of the gonadotrophins, then it is interesting that lipid peroxidation of polyunsaturated fatty acids (which increases with age) can be intimately involved in loss of progesterone forming ability by human steroidogenic tissues.(10) That is, aging decreases the ability of certain brain cells to inhibit the pituitary gonadotrophins, and it also tends to decrease the steroidogenic tissues' ability to produce the regulatory steroids.

After menopause, estrogen is produced less by the ovary than by other tissues, including fat cells. Breast cancer cells can produce their own estrogen. This means that estrogen is one of the "cancer hormones" which, secreted by the tumor, promotes the growth of the tumor and also has a systemic pro-cancer action. Ovarian tumors, too, can cause great systemic hormonal imbalances, which should be investigated routinely in a physiological approach to the disease. After menopause, estrogen is largely produced by conversion of "androgenic" steroids from the adrenal glands. It would be desirable to be able to inhibit the conversion of the adrenal steroid precursor to estrogen. Newton, et al.(11)

showed that progesterone inhibits the conversion of the precursor to estrogen, and P.K. Siiteri showed a similar effect for thyroid hormone.

A diet low in polyunsaturated fats facilitates thyroid hormone secretion, transport, and tissue response to it, and would minimize the stress-related or age-related inhibition of progesterone formation by lipid peroxidation. Vitamin E and vitamin A also protect against lipid peroxidation, and vitamin A is specifically involved in progesterone synthesis. Vitamin A also has a variety of anti-estrogen functions,(12) that are often considered to be relevant to protection against cancer.(13)

All of these dietary and hormonal approaches to normalizing the pituitary gonadotrophins and controlling ovarian cell division are things which also tend to optimize the immune response. A slight deficiency of iron is probably protective against cancer, since there are several ways that iron can promote cancer, apart from its role in damage to the immune system and the steroidogenic system by lipid peroxidation.(14)

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Townsend Letter for Doctors & Patients.

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By Ray Peat
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Ray Peat's Newsletter

A New Approach to Detoxifying

Ernest Krebs, the inventor of the laetrile cancer treatment, compiled some interesting facts about cancer metabolism. Noting that cancer cells are typically fairly deficient in the enzyme rhodanese, which protects cells against cyanide poisoning if the dose isn't too high, he theorized that cyanide might selectively kill the relatively unprotected cancer cells, especially if the dose could be concentrated near the cancer.[1]

While amygdalin releases a large proportion of its cyanide in the bowel, his original laetrile, the glucuronide form, should liberate its cyanide largely in areas of inflammation or injury, including cancers.

Although cancer cells have a low level of rhodanese, they typically have intense glycolytic metabolism which compensates for their respiratory defect. Otto Warburg and Dean Burk showed pretty decisively that "defective respiration" exists in all of the cancers studied.

Maybe we can see a different meaning in the same facts.

What if the respiratory defect that was so carefully documented by Warburg and Burk is the result of damage to the detoxifying rhodanese enzyme? If cyanide is a general threat to respiration, a deficiency of rhodanese would allow it to damage respiration, and this, according to Warburg, should lead either to cell death or, if the cell can adapt adequately, to the production of cancer.

Rhodanese occurs in all animals, and seems to be localized inside the mitochondria. Although it does handle some other sulfur reactions, its basic function is thought to be the elimination of cyanide, by the addition of sulfur, forming thiocyanate. Thiocyanate is fairly non-toxic, though it can be broken down into cyanide again, and it does have a significant anti-thyroid effect.

Herbivores eat many plants that are rich in cyanide-releasing compounds, so it is logical that they should be equipped with rhodanese. But carnivores are not exposed to these toxic vegetable products, so it is hard to explain why they have the enzyme. The fact that serum albumin, which has many detoxifying functions, carries sulfane sulfur, the form which is used by rhodanese to react with cyanide, supports the idea that rhodanese is involved in the elimination of cyanide.

People who smoke or eat significant amounts of plant material are exposed to cyanide, but the fact that the rhodanese enzyme exists in all animals, whether their diet includes "cyanophoric" compounds or not, suggests that we might want to consider other possible sources of cyanide.

People studying lipid peroxidation in liver cell extracts noticed that carbon monoxide was being produced. Many people have observed that stressed cells emit ammonia.[2] There are industrial processes which use ammonia and carbon monoxide to produce cyanide, using a metal as catalyst.[3] Since carbon monoxide binds to metal atoms, it might be held in a form which reacts easily with ammonia. Then during stress, which causes both lipid peroxidation and ammonia formation, rhodanese would be needed to protect the respiratory cytochromes from the cyanide, which would otherwise inhibit respiratory energy production, and other processes involving the cytochromes. Within the mitochondria, a cytochrome P-450 converts cholesterol to pregnenolone. The loss of both energy and steroid hormones would have major consequences. Outside the mitochondria, many other cytochrome functions will be inhibited; other types of enzymes would also be inhibited.

Another possible source of cyanide would be bacteria in the intestine; methane and ammonia are other possible starting materials for making cyanide. The urea cycle itself, inside the mitochondria, is a conceivable source.

Even if dietary plant material turns out to be the main source of cyanide, it is important to be able to eliminate it efficiently.

When flowers of sulfur is taken orally, some of it becomes available for use in the rhodanese system. It might be less irritating and more effective to use a form of sulfur which is chemically more available, namely thiosulfate. (My thoughts on light removing carbon monoxide from cytochromes led me to think about photography; sodium thiosulfate is used to clear the photographic emulsion, removing the silver which was not exposed to light. In that sense, its activity as a reductant is equivalent to light's action).

In acute cyanide poisoning, a large dose of sodium thiosulfate (12 grams) is injected rapidly; it is poorly absorbed when taken orally. I decided to try small oral doses, about 50 mg. a few times per day. It has improved my tolerance for chocolate and wheat, which I still reacted to in spite of using pregnenolone, which was permitting me to eat many other foods that earlier would have caused migraines and asthma. Pregnenolone seems to stabilize the cytochromes physically, while rhodanese (with sulfur) restores their chemical activity. Some druggists still sell sodium thiosulfate as a treatment for skin diseases. It has been used to treat arthritis, which would be logical if it is able to increase formation of pregnenolone and the various steroid hormones.

Since very high levels of cortisone destroy the detoxifying cytochrome enzymes,[4] the use of thiosulfate – to restore any of the remaining cytochromes which might be blocked by cyanide – would seem to be appropriate as part of an anti-stress approach to disease. As far as I know, it hasn't been tried as part of cancer therapy; improving a cancer cell's viability might, as many people believe, reduce its virulence, but it might just make it a more energetic cancer cell.

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Ray Peat

Abnormal Cells in the Uterine Cervix

The membranes of the mouth and of the uterine cervix are very similar, and both are susceptible to development of a supposedly precancerous condition, called leukoplakia. Every winter since I moved to Oregon, I developed areas on the inside of my cheeks where they met my teeth, that became spongy and white, and tended to be imprinted with the shape of my teeth, bulging in a way that caused me to bite my cheek frequently. When I learned that vitamin A would control my dandruff and acne, I then noticed that it also normalized my mouth membranes. A dentist noticed my spongy white spots one winter when I hadn't been taking vitamin A, and gravely warned me that it was a precancerous condition, leukoplakia (sometimes called psoriasis buccalis, or dyskeratosis), and that I should have it checked by a doctor frequently. I went home and took vitamin A, and it was gone within a few days. This experience increased my interest in leukoplakia and led me to read more about it. Because of the similarity of cell type in the cervix and in the mouth, I suggested to a friend that she try vitamin A when her doctor told her that she had cervical leukoplakia, and it cleared up right away.

Since the beginning of the century, it has been known that estrogen is carcinogenic, and by the 1940s it was clear that the hormone of the corpus luteum, progesterone, opposes estrogen's effects, and that it consistently prevented estrogen-induced cancers, and sometimes cured them. In the 1950s, it was learned that vitamin A and estrogen have opposite effects, for example, when applied locally to the skin.1 It was found that, to a very great extent, progesterone could substitute for vitamin A, meaning that a very large fraction of the vitamin A used by the body is used up in making progesterone, from which the other steroid hormones are made.

Considering these facts, it seemed apparent that optimal treatment of leukoplakia would involve a program to lower the chronic background level of estrogen, while promoting progesterone synthesis. It happens that the body spontaneously moves in that direction, if given the right support. With adequate protein (eggs, milk, cheese, shellfish, liver, etc.), the liver removes estrogen from the blood entirely on its first passage through the liver, in an otherwise healthy organism. In hypothyroidism, the liver metabolism slows, allowing estrogen to accumulate; also, hypothyroidism appears to allow ovarian cysts to develop and to secrete additional estrogen. While the thyroid hormone promotes the elimination of estrogen, it happens to be essential for the production of progesterone. Vitamin A (with cholesterol) is consumed at a high rate by the corpus luteum, when there is adequate thyroid hormone. However, carotene also tends to be accumulated by the corpora lutea, because of its chemical similarity to

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vitamin A – it is probably a mixture of vitamin A and carotene that gives the corpus luteum its yellow color –but carotene seems to compete with vitamin A for the active synthetic sites, with the result that too much carotene is toxic to the corpus luteum, and is a fairly common cause of failure to have menstrual cycles. Both vitamin A and carotene, like any unsaturated oil, will tend to inhibit the thyroid, so it is important to balance supplements of vitamin A and thyroid; a sluggish thyroid will more easily be suppressed by large doses of vitamin A, but a high level of thyroid activity causes vitamin A to be used more quickly. It is an interesting expression of this biological relationship that one blood protein carries both vitamin A and thyroid hormone.

To back up this basic process of hormone balancing, there are a few things that can be done besides providing animal protein, vitamin A and thryoid. Vitamin E causes vitamin A to be used more efficiently, and besides taking about 100 units orally, a mixture of vitamin E, vitamin A, and progesterone can be applied directly to the cervical membrane. In rapid cell division, and in estrogen excess, folic acid and other B vitamins are used rapidly, so a supplement might be useful. I have usually suggested a dose of one to ten milligrams of folic acid daily for a few weeks, with liver two or three times a week for the other vitamins. Magnesium is not retained well during stress or in hypothyroidism, so a supplement of several hundred milligrams daily is desirable; epsom salts in orange juice is well assimilated and magnesium oxide should not be used because it is not absorbed. Plenty of bright light helps to maintain progesterone synthesis. Vitamin C and zinc are needed, but will probably be provided by the meat, liver, oysters and orange juice which will provide many of the calories; beans, seeds, sprouts, and seed oils, and raw broccoli or cabbage should be avoided, because they can disrupt the hormone balance.

I personally had contact with 35 women who were advised to have a hysterectomy because of abnormal cells found in Pap smears or biopsies, but who wanted to try this approach for a month or two. All of those women had normal tests when they went back to the doctor, usually in two months. Later, I heard that groups had been formed to teach the method, but I haven't heard whether the results continue to be 100%.

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Ray Peat's Newsletter

Natural Immunity and Viral Infections

W F. Koch worked in Moses Gomberg's lab, where free radicals were first observed. Koch soon constructed a theory of natural immunity against virus and cancer, based on his belief in the existence of biological free radicals, able to oxidize virus particles and carcinogenic molecules. Koch believed that allergies were an early sign of the failure of this free radical oxidation system.[1]

Albert Szent-Györgyi worked out some of Koch's ideas, and in the process discovered vitamin C (which has a free radical state), and explored many other energy exchange processes, including free radical activation by biological pigments.[2]

Both of these men argued that there is a special interaction between biological structure and the activated electronic state, and that both structural and electronic properties of molecules are involved in their toxic or therapeutic functions.

This model of cell structure and function leads to the expectation that any substance is likely to have a broad range of effects, acting on many different cell types, and promoting or suppressing cell functions, depending on the cell's type and its present state.

In this view, the living material is not an ordinary liquid, but is deeply structured, somewhat like a liquid crystal, and this structure is subject to many physical influences, in the process of adapting to a changing environment.[3]

Newer techniques are letting us visualize more of this finely structured cellular system, and it has been found that many types of virus replicate themselves while attached to the cell mesh-work.4 Alterations in the mesh-work and the adjoining water will obviously affect the ability of the virus to multiply.

The highest energy states of the cell tend to exclude water soluble substances, and to absorb oil soluble materials. The components of a virus have very specific affinities for water and oil, and they can be assembled only in a very special solvent environment. As mentioned above, a substance which modifies any type of cell will modify others. The high energy state of a cell is an electrically "hyperpolarized" state, and for a nerve cell this is an inhibited, quiet state.

Camphor

There is a long history of anesthetic substances being used to treat viral diseases. Abrams, in a 1910 textbook, described the use of chloroform to cure a viral disease in a horse. Camphor, besides being used as a local anesthetic and a heart stimulant, has been used to treat influenza and other systemic diseases,[5] and is one of the oldest topical treatments for herpes sores. More recently, a veterinarian reported curing an "incurable" virus disease in a dog with an anesthetic dose of ether.

Adamantane, which can be extracted from petroleum, is a close structural analog of camphor, and smells like camphor. With the addition of a nitrogen atom, it is water soluble, and is an effective anti-viral agent,

There is a long history of anesthetic substances being used to treat viral diseases.

and is also widely used in treating Parkinson's disease (its function is cholinolytic),[6] and more recently is being used in preventing withdrawal symptoms in cocaine addiction.[7] It is not metabolized, and does not present the genetic risk that has recently been recognized for other anti-viral agents which disrupt viral DNA.[8]

The fact that the body is well supplied with substances which – at a slightly higher concentration – are anesthetics, and which are depleted by the stresses which predispose to viral infections, suggests that they may normally have a camphor-like anti-viral activity. Some of these substances, the anesthetic steroids, have been found to prevent some viral infections,[9] and they also have a wide range of anti-toxic effects.[10] Pregnenolone, progesterone, DHEA, and pregnanediol are all good candidates as anti-viral drugs, but etiocholanolone – which also produces fever[11] – is the most interesting of the group.

It is well-known that stress, acting mainly through the glucocorticoid hormones, damages immunity by destroying thymus cells. The anesthetic steroids, especially progesterone, normally reduce the need for secretion of cortisol, but also act as a protective buffer against the damaging effects of cortisol.

Although a physiologically balanced amount of cortisol induces enzymes of detoxification, for example in the intestine, an unopposed excess causes destruction of these enzymes, eliminating much of the intestine's barrier function, and leading to allergies.[12] This action of cortisol against the thymus and against the bowel's detoxifying enzymes very likely accounts for the common association of allergies with virus infections. Since cortisol has a destabilizing, pro-convulsant effect on the nervous system, there are likely to be psychological symptoms – anything from compulsive behavior to depression or seizures – associated with the other chronic conditions.

In the last century, it was observed that digitoxin (a natural steroid derivative) lowered the fever caused by enteritis.[11] This is probably another example of a catatoxic function, a protective function common to many steroids, and probably worked by way of stabilizing the detoxifying enzymes and preventing the absorption of endotoxin.[13] Endotoxin is known to destabilize and inactivate the bowel's detoxifying enzymes, just as an overdose of cortisol does.[14]

Biological Erasers

Although it is important to be aware of the deadly effects of chronic, unopposed exposure to cortisol (and estrogen and prolactin), these hormones which cause atrophy and loss of function in various tissues also have a creative function. I have elsewhere called them the biological "erasers," the hormones of new beginnings.[15] In the case of cortisol, it might be useful to compare its effects on tissue cells to the process of winnowing wheat, in which the chaff is blown away while the grain is retained. I think there is a mechanism, as proposed by Meerson, in which a functional load preserves the cells and systems which are needed in the present environment, while idle cells are eliminated or reduced by cortisol's

catabolic action.[16] In this view, intermittent exposure to these hormones would improve resistance, but continuing uninterrupted exposure will destroy resistance.

Adequate energy, for example as available glucose, is protective against cortisol-induced catabolism. White blood cells can protect themselves by metabolizing cortisol in the presence of sufficient glucose.[17]

Some of the consequences of stress are not catabolic. When the detoxifying enzymes have been lost, then bowel toxins block other basic enzyme systems, leading for example to slowed protein turnover[18] and decreased activity of superoxide dismutase.[19] The consequent increase of lipid peroxidation will decrease steroid synthesis.[20] Stress also leads to the production of intracellular toxins, including ammonia and carbon monoxide, which tend to perpetuate the blocked state.

Just as with the anesthetic substances which modify the physical state of the cell, retarding viral replication, the oxidative protective system has several points at which intervention is possible to support detoxification, and to promote protein turnover.

Injecting Enzymes

Although natural promotion of the enzymes which degrade proteins and nucleic acids will help to shift the equilibrium away from virus production, recent research shows that it can be therapeutic to inject enzymes (nucleases, both DNAase and RNAase) which degrade viral nucleic acids.[21] Using labelled enzymes, it has been demonstrated that virus and enzyme can enter the cytoplasm in the same vesicle. In herpetic keratitis, the enzyme is used as drops and also injected under the conjunctiva, and in infectious mononucleosis and viral encephalitis it is injected intramuscularly.[21] In treating a viral paralysis of bees, the enzyme is administered as an aerosol. It was found that treatment increased the viability and productivity of outwardly healthy bees, apparently by curing a latent viral infection.[21]

While W.F. Koch was interested in the body's own oxidative free radical system of destroying toxins and pathogens, he studied several natural quinones found in medicinal plants. Recent work has found that phototoxins extracted from plants can kill mouse-cytomegalovirus without damaging the mouse cells.[21] These researchers selected chemicals which do not disrupt genetic material, recognizing the probability of serious side effects.

Although injected enzymes and plant toxins are safer than some current chemotherapies, the basic approach to controlling viral diseases should be to support natural immunity, by maintaining energy production at a high level, by unblocking and stabilizing the detoxifying enzymes, including mono-oxygenases, proteolytic enzymes, SOD, and nucleases, and by avoiding prolonged catabolic states. Many natural substances are available which promote these ends, without risk.

While this approach supports the known mechanism of the immune system, including protection of thymus cells and activation of the various white cell mechanisms of attack, it has the novel feature of altering cells physically to retard viral assembly, increasing their exposure to nucleases, proteases, and mono-oxygenases; that is, it mobilizes immune processes in cells which are not part of the immune system. By eliminating stress-induced susceptibility, it systematically shifts the balance toward normal functioning, and away from parasitic diversion of the organism's resources.

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All manuscripts for publication are to be typed and double spaced.

A reference sentence has a reference number at end.[3]

References for articles are written as follows:

3. Garner DM, Garfinkel PE, Socio-cultural factors in the development of anorexia nervosa. *Psychol Med* 1980; 10:647-56.

References for books are written as follows:

3. Benson, Herbert, M.D., *The Mind/Body Effect,* Simon and Schuster, NY, 1979.

Multiple Sclerosis & Other Hormone-Related Brain Syndromes

Since I am trying to discuss a complex matter in a single article, I have separately outlined the essential technical points of the argument in a section at the beginning, then I explain how my ideas on the subject developed, and finally there is a glossary. If you start with "Short-day brain stress," "Estrogen's effects," and "Symptoms and therapies," you will have the general picture, and can use the other sections to fill in the technical details

The Argument:

The hormones pregnenolone, thyroid, and estrogen are involved in several ways with the changes that occur in multiple sclerosis but no one talks about them.
The process of myelination is known to depend on the thyroid hormone The myelinating cells are the oligodendroglia (oligodendrocytes) which appear to stop functioning in MS (and sometimes to a milder degree in Alzheimer's disease, and other conditions). The cell's absorption of thyroid hormone is influenced by dietary factors.
The oligodendrocytes are steroid-producing cells,(1) and steroidogenesis is dependent on thyroid hormone, and on thyroid-dependent respiratory enzymes and on the heme-enzyme P-450 scc, which are all sensitive(2) to poisoning by carbon monoxide and cyanide The steroid produced by the oligodendrocytes is pregnenolone, which is known to have a profound anti-stress action,(3) and which appears to be the main brain-protective steroid.
Lesions resembling those of MS can be produced(4) experimentally by carbon monoxide or cyanide-poisoning. The lesions tend to be associated with individual small blood vessels and are likely to contain clots. (Since all animals have enzymes to detoxify cyanide, this poison is apparently a universal problem and can originate in the bowel. "Detoxified" cyanide is still toxic to the thyroid.)
Pregnenolone and pogesterone protect against nerve damage(5) by the excitotoxic amino acids (glutamic acid, aspartic acid, monosodium glutamate, aspartame, etc.), while estrogen(6) and cortisol(7) are nerve-destroying, acting through the excitotoxic amino acids. Excitotoxins destroy certain types of nerve, especially the dopaminergic and cholinergic types, leaving the noradrenergic types,(8) paralleling the changes that occur in aging. The clustering of oligodendrocytes around deteriorating nerve cells could represent an adaptive attempt to provide pregnenolone to injured nerve cells.
The involvement of hormones and environmental factors probably accounts for the intermittent progress of multiple sclerosis. To the extent that the environmental factors can be corrected, the disease can probably be controlled.

Short-Day Brain Stress

Shortly after I moved from Mexico to Montana, one of my students, a 32-year old woman, began having the same sensory symptoms her older sister had experienced at the same age, at the onset of multiple sclerosis Vertigo and visual distortions of some sort made her consider withdrawing from the university. I'm not sure why she tried eating a whole can of tuna for lunch a couple of days after the onset of symptoms, but it seemed to alleviate the symptoms, and she stayed on a high protein diet and never had a recurrence. She told me some of the lore of MS: That it mostly affects young adults between the ages of 20 and 40, that it is common in high latitudes and essentially unknown in the tropics, and that it is sometimes exacerbated by pregnancy and stress. (Later, I learned that systemic lupus erythematosis and other "auto-immune" diseases also tend to occur mainly during the reproductive years).

Having enjoyed the mild climate of Mexico, I became very conscious of the harm done to us by northern winters, and began developing the idea of "winter sickness." In 1966-67 allergies, PMS, weight gain, colitis, and arthritis came to my attention as winter-related problems, and I assumed that the high-latitude incidence of MS related to what I was seeing and experiencing. Studies in Leningrad began revealing that mitochondria are injured during darkness, and repaired during daylight. I observed that hamsters' thymus glands shrank in the winter and regenerated in the summer; shrinkage of the thymus gland is a classical feature of stress, and usually reflects the dominance of cortisone, though estrogen and testosterone also cause it to shrink. Winter's darkness is stressful in a very fundamental way, and like any stress it tends to suppress thyroid function. In the hypothyroid state, any estrogen which is produced tends to accumulate in the body, because of liver sluggishness.

I began to see that PMS could be controlled by certain things -- extra light, supplements of sodium and magnesium, high quality protein, and correction of deficiencies of thyroid and progesterone. In working on my dissertation, I saw that tissue hypoxia (lower than optimal concentrations of oxygen in the blood) may result from estrogen excess, vitamin E deficiency, or aging. There is a close biological parallel between estrogen-dominance and the other hypoxic states, such as stress/shock, and aging.

Estrogen's Effects

As an amateur portrait painter, I had been very conscious of the blue aspect that can often be seen in the skin of young women. In pale areas, the color may actually be blue, and in areas with a rich supply of blood, such as the lips, the color is lavender during times of high estrogen influence -- around ovulation and puberty, for example. During these times of estrogen dominance, the blood is not only poorly oxygenated, but it has other special properties, such as an increased tendency to clot. The Shutes' work in the 1930s began with the use of vitamin E to antagonize estrogen's clot-promoting tendency, and led them to the discovery that vitamin E can be very therapeutic in heart disease. More recently, it has been found that men with heart disease have abnormally high estrogen,(9) that women using oral contraceptives have higher mortality from heart attack,(10) and that estrogen tends to promote spasm of blood vessels.(11) (These reactions are probably related to the physiol ogy of menstruation, in which progesterone withdrawal causes spasms in the spiral arteries of the uterus, producing endometrial anoxia and cell death.)

In toxemia of late pregnancy, or eclampsia, the exaggerated clotting tendency caused by excess estrogen (or by inadequately opposed estrogen, i.e., progesterone deficiency), can cause convulsions and strokes. Vascular spasms could be involved here, too. The stasis caused by the vasospasm would facilitate clotting. (Vascular spasm has been observed in epilepsy, too. Epilepsy can be brought on by the premenstrual excess of estrogen, and in that situation there is no evidence that clotting is involved. Leakage of hemoglobin out of red cells can cause vasospasm, so bleeding, clotting, strokes, and seizures can interact complexly.) The brains of women who have died following eclampsia show massive clotting in the blood vessels, and their livers are characteristically injured, with clots.(12)

Tom Brewer and others have shown very clearly that malnutrition, especially protein deficiency, is the cause of toxemia of late pregnancy.

Various researchers have demonstrated that the plaques of MS usually occur in the area served by a single blood vessel,(13, 14) and some have suggested that clotting is the cause. MS patients have been found to have an abnormal clotting time, and it has been suggested that an altered diet might be able to correct the clotting tendency.

Studies in animals have shown clearly that a protein deficiency increases the fibrinogen content of blood. (Field and Dam, 1946.) Other factors that increase blood clotting are elevated adrenaline and cortisone. Protein deficiency causes an adaptive decrease in thyroid function, which leads to a compensatory increase in adrenaline and cortisone. The combination of high estrogen with high adrenaline increases the tendency for both clots and spasms of the blood vessels.(11)

In experimental poisoning of animals with carbon monoxide or cyanide, the brain lesions resembling MS include blood clots. The patchy distribution of these spots in

the brain suggests that the clotting is secondary to metabolic damage in the brain. Presumably, the same would be true in ordinary MS, with clots and spasms being induced in certain areas by metabolic abnormalities in brain cells. The injured cells that are responsible for myelination of nerve fibers are steroid-forming cells. A failure to secrete their protective pregnenolone could cause a local spasm of a blood vessel. The circulatory problem would exacerbate the respiratory problem. Steroid production is dependent on NADH and NADPH, and so requires adequate energy supplies and energy metabolism. The phenomenon of blood-sludging, studied by M. Knisely at the University of Chicago in the 1930s and 1940s, is apparently a general result of decreased energy metabolism, and is likely to be a factor in energy-and-circula tory vicious circles.

Symptoms and Therapies

Around 1976 I met a woman in her mid-30s who heard about my work with progesterone in animals. She had been disabled by a brain disease that resembled MS or Devic's disease, inflammation of the optic nerves. It would sometimes cause blindness and paralysis that persisted for weeks at a time. During remissions, sometimes using a wheelchair, she would go to the medical school library to try to understand her condition. She came across Katherina Dalton's work with progesterone, and convinced a physician to give her a trial injection. Although she had trouble finding people who were willing to give her progesterone, her recovery was so complete that she was able to climb stairs and drive her car, and she came to my endocrinology class and gave a very good (and long) lecture on progesterone therapy. Although her sensory and motor functions became normal, she remained very fat, and chronically suffered from sore areas on her arms and legs that seemed to be abnormal blood vessels, pos sibly with phlebitis. She appeared to need thyroid hormone as well as larger amounts of progesterone, but never found a physician who would cooperate, as far as I know.

In the late 1970s I was seeing a lot of people who had puzzling health problems. In a period of two or three years, there were five people who had been diagnosed by neurologists as having Multiple Sclerosis. In talking to them, it seemed clear that they had multiple symptoms of hypothyroidism. They weren't severely disabled. Since they weren't fat or lethargic, their physicians hadn't thought they could be hypothyroid. When they tried taking a thyroid supplement, all of their symptoms disappeared, including those that had led to their MS diagnosis. One of the women went to her doctor to tell him that she felt perfectly healthy since taking thyroid, and he told her to stop taking it, because people who have MS need a lot of rest, and she wouldn't get enough rest if she was living in a normally active way. The assumption seemed to be that the diagnosis was more important than the person. (When I refer to a "thyroid supplement" I mean one that contains some T3. Many people experien ce "neurological symptoms" when they take thyroxine by itself. Experimentally, it has been found to suppress brain respiration, probably by diluting the T3 that was already present in the brain tissue.)

Metabolism of the Oligodendrocytes

The rate-regulating step in steroid synthesis involves the entry of cholesterol into the mitochondria, where the heme-enzyme P-450 scc then removes the side-chain of cholesterol (by introducing oxygen atoms), to produce pregnenolone. This enzyme can be poisoned by carbon monoxide or cyanide, and light can eliminate the poison;(18) this could be one aspect of the winter-sickness problem.

Peripheral nerves are myelinated by essentially the same sort of cell that is called an oligodendrocyte in the brain, but outside the brain it is called a Schwann cell. It is easier to study the myelin sheath in peripheral nerves, and the electrical activity of a nerve is the most easily studied aspect of its physiology. Certain experiments seemed to indicate a "jumping" (saltatory) kind of conduction along the nerve between Schwann cells, and it was argued that the insulating function of the myelin sheath made this kind of conduction possible. This idea has become a standard item in physiology textbooks, and its familiarity leads many people to assume that the presence of myelin sheaths-in the brain serves the same "insulating" function

For a long time it has been known that heat production during nerve conduction reveals a more continuous mode of conduction, that doesn't conform to the idea of an electrical current jumping around an insulator. Even if the myelin functioned primarily to produce "saltatory conduction" in peripheral nerves, it isn't clear how this process could function in the brain. I think of the issue of "saltatory conduction at the nodes of Ranvier" as another of the fetish ideas that have served to obstruct progress in biology in the United States. A more realistic approach to nerve function can be found in Gilbert Ling's work. Ling has demonstrated in many ways that the ruling dogma of "cell membrane" function isn't coherently based on fact. He found that hormones such as progesterone regulate the energetic and structural stability of cells. Many people, unaware of his work, have felt that it was necessary to argue against the idea that there are anesthetic steroids with generalized protect ive functions, because of their commitment to a textbook dogma of "cell membrane" physiology.

I think the myelinating cells do have relevance to nerve conduction, but I don't think they serve primarily as electrical insulators. If the adrenal cortex were inside the heart, it would be obvious to ask whether its hormones aren't important for the heart's function. Since the oligodendrocytes are steroid-synthesizers, it seems obvious to ask whether their production of pregnenolone in response to stress or fatigue isn't relevant to the conduction processes of the nerves they surround.

Old Age

A biologist friend of mine who was about 85 became very senile. His wife started giving him thyroid, progesterone, DHEA and pregnenolone, and within a few days his mental clarity had returned. He continued to be mentally active until he was 89, when his wife interfered with his access to the hormones.

In old age the brain steroids fall to about 5% of their level in youth. Pregnenolone and DHEA improve memory in old rats, and improve mood stability and mental clarity of old people. Pregnenolone's action in improving the sense of being able to cope with challenges probably reflects a quieting and coordinating of the "sequencing" apparatus of the forebrain, which is the area most sensitive to energy deprivation. This is the area that malfunctions in hyperactive and "dyslexic" children. Weakening of the sequencing and sorting processes probably explains the common old-age inability to extract important sounds from environmental noise, creating a kind of"confusion deafness." Insomnia, worry and "restless legs" at bedtime are problems for many old people, and I think they are variations of the basic energy-depletion problem.

The oligodendrocytes were reported (Hiroisi and Lee, 1936) to be the source of the senile plaques or amyloid deposits of Alzheimer's disease.(16) Hiroisi and Lee showed the cells in different stages of degeneration, ending with translucent "mucoid" spots that stained the same as amyloid, the material in the senile plaques. This type of cell also appears to form a halo or crown around degenerating nerve cells -- possibly in a protective reaction to provide the nerve cell with any pregnenolone the oligodendrocytes are able to make. The oligodendrocytes, the source of the brain steroids (that people previously believed came from the adrenals and gonads, and were just stored in the brain), myelinate nerve fibers under the influence of thyroid hormone.(17) Thyroid is responsible for both myelination and hormone formation. In old age, glial cells become more numerous, and nerve cells become structurally and functionally abnormal, but usually there is no problem with the formation of m yelin. In MS, the problem is just with myelination, and there are no senile plaques or defects in the nerve cells themselves.

These differences suggest the possibility that Alzheimer's disease involves a specific premature loss of brain pregnenolone production, but not of thyroid. Recent work suggests a central role for pregnenolone and progesterone in the regulation of consciousness,(18) and possibly in the brain's detoxifying system. Elsewhere, I have suggested that vitamin A deficiency might cause the excessive production of the "amyloid" protein. A vitamin A deficiency severely inhibits steroid synthesis. (It is used so massively in steroid synthesis that a progesterone supplement can prevent the symptoms of vitamin A deficiency.) I suspect that vitamin A is necessary for the side-chain cleavage that converts cholesterol to pregnenolone. Iron-stimulated lipid peroxidation is known to block steroid formation, and vitamin A is very susceptible to destruction by iron and oxidation. Iron tends to accumulate in tissues with aging. Gajdusek has demonstrated that brain deterioration is associated with the retention of whatever metal happens to be abundant in the person's environment, not just with aluminum. (One type of glial cell is known for its metal-binding function, causing them to be called "metallophils.") According to Gajdusek, "calcium and other di- and trivalent elements" are "deposited as hydroxyapatites in brain cells" in brain degeneration of the Alzheimer's type.(19)

Even early forms of Alzheimer's disease begin at an age when the youth-associated steroids have begun to decline. If MS involves a deficiency of thyroid (or of T3 within the oligodendrocytes, where T3 normally can be made from thyroxine; many things, including protein deficiency, can block the conversion of T4 to T3), those cells would necessarily be deficient in their ability to produce pregenolone, but in young people the brain would still be receiving a little pregnenolone, progesterone, and DHEA from the adrenals and gonads. This relatively abundant youthful supply of hormones would keep most of the body's organs in good condition, and could keep the bodies of the major brain cells from deteriorating. But if proper functioning of the nerve fibers requires that they be fed a relatively high concentration of pregnenolone from their immediately adjacent neighbors (with the amount increasing during stress and fatigue), then their function would be impaired when they had to depen d on the hormones that arrived from the bloodstream.

For many years it has been recognized that the brain atrophy of "Alzheimer's disease" resembles the changes seen in the brain in many other situations: The traumatic dementia of boxers; toxic dementia, the slow-virus diseases; exposure of the brain to x-rays;(20) ordinary old age; and in people with Down's syndrome who die around the age of thirty.

In menopause, certain nerve cells have lost their ability to regulate the ovaries, because of prolonged exposure to estrogen.(6) The cells that fail as a result of prolonged estrogen exposure aren't the same cells that fail from prolonged exposure to the glucocorticoids,(7) but they have in common the factor of excitatory injury.

Since people who experience premature menopause are known to be more likely than average to die prematurely, it is reasonable to view menopause as a model of the aging process. It is now well established that progesterone fails to be produced at the onset of menopause (the first missed period, increased loss of calcium, symptoms such as hot flashes, etc.), and that estrogen continues to be produced at monthly intervals for about four years. The essential question for aging, in the present context, is why the anesthetic steroids are no longer produced at a rate that allows them to protect tissues, including brain cells, from the excitotoxins. Using menopause as a model for aging, we can make the question more answerable by asking why progesterone stops being produced.

During stress, we are designed not to get pregnant, and the simplest aspect of this is that ACTH, besides stimulating the adrenals to produce stress-related hormones, inhibits the production of progesterone by the ovary. Other stress-induced factors, such as increased prolactin and decreased thyroid, also inhibit progesterone production. Stress eventually makes us more susceptible to stress. Menopause and other landmarks of aging simply represent upward inflections in the rate-of-aging curve. Individual variations in type of stress, hormonal response and diet, etc., probably govern the nature of the aging process in an individual.

The amphetamine-like action of estrogen, which undoubtedly contributes to the general level of stress and excitotoxic abuse of nerve cells, is probably the only "useful" facet of estrogen treatment, but a little cocaine might achieve the same effect with no more harm, possibly less. The toxicity of catecholamines has been known for over 30 years, and conversion to catechol-estrogens which increase the activity of brain catecholamines. Estrogen's powerful ability to nullify learning seems never to be mentioned by the people who promote its use. The importance of a good balance of brain steroids for mood, attention, memory, and reasoning is starting to be recognized, but powerful economic forces militate against its general acceptance.

Since the brain is the organ that can allow us to adapt without undergoing stress in the hormonal sense, it is very important to protect its flexibility and to keep its energy level high, so it can work in a relaxed way. It is the low energy cellular state that leads to the retention of calcium and iron, and to the production of age pigment, and other changes that constitute the vicious circle of aging. And mental activity that challenges obsession and rigidity might be the most important brain energizer. Pseudo-optimism, humor-as-therapy, has a certain value, but a deeper optimism involves a willingness to assimilate new information and to change plans accordingly.

Supplements

Nutritional supplements that might help to prevent or correct these brain syndromes include: Vitamin E and coconut oil; vitamin A; magnesium, sodium; thyroid which includes T3; large amounts of animal protein, especially eggs; sulfur, such as magnesium sulfate or flowers of sulfur, but not to take continuously, because of sulfur's interference with copper absorption; pregnenolone; progesterone if needed. Bright light, weak in the blue end of the spectrum and with protection against ultraviolet, activates respiratory metabolism and quenches free radicals. Raw carrot fiber and/or laxatives if needed; charcoal occasionally for gas or bowel irritation. Coconut oil serves several purposes. Its butyric acid is known to increase T3 uptake by glial cells. It has a general pro-thyroid action, for example by diluting and displacing antithyroid unsaturated oils, its short-and medium-chain fatty acids sustain blood sugar and have anti-allergic actions, and it protects mitochondria against s tress injury.

In 1979, a woman whose husband was suffering from advanced Amyotrophic Lateral Sclerosis (ALS) asked me if I had any ideas for slowing his decline. I described my suspicion that ALS involved defective metabolism or regulation of testosterone. In some tissues, testosterone is selectively concentrated to prevent atrophy, and ALS is a disease of middle-age, when hormone regulation often becomes a special problem. In the late 1970s, there was discussion of a higher incidence of ALS in males, and especially in athletes I told her about progesterone's general protective effects, its antagonism to testosterone, and its prevention of atrophy in various tissues. She decided to ask her doctor to try progesterone for her

husband Later, I learned that her husband had gone into a very rapid decline immediately after the injection, and died within a week; the physician had given him testosterone, since, he said, "testosterone and progesterone are both male hormones." Besides making me more aw are of the problems patients have in communicating with physicians, this tended to reinforce my feeling that a hormone imbalance is involved in ALS. Although I haven't written much about testosterone's toxicity, Marian Diamond's work showed that prenatal testosterone is similar to prenatal estrogen, in causing decreased thickness of the cortex of the brain; both of those hormones oppose progesterone's brain-protecting and brain-promoting actions.

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Glossary

Amyloid is the old term for the "starchy" appearing (including the way it stains) proteins seen in various diseases, and in the brain in Alzheimer's disease.
Cytochrome P450 scc. The cytochromes are "pigments," in the same sense that they contain the colored "heme" group that gives hemoglobin its color. P450 means "protein that absorbs light at a wavelength of 450." The scc means "side-chain cleaving," which refers to the removal of the 6 carbon atoms that distinguish cholesterol from pregnenolone. Other Cyt P450 enzymes are important for their detoxifying oxidizing action, and some of these are involved in brain metabolism.
Glial means "glue-like," and glial cells are mostly spidery-shaped cells that used to be thought of as just connective, supportive cells in the brain.
Mitochondria (the "thread-like bodies") are the structures in cells which produce most of our metabolic energy by respiration, in response to the thyroid hormones.
Mucoid refers to a mucoprotein, a protein which contains some carbohydrate. A glycoprotein, usually not intended as a precise term.
Myelination. Myelin is a multilayered enclosure of the axons (the long processes) of nerve cells, composed of proteins and complex lipids, including cholesterol. The layered material is a flat, thin extension of the cytoplasm of the oligodendroglial cells.
Oligodendrocytes are one of the kinds of glial (or neuroglial) cells, and structurally they are unusual in having sheet-like, rather than just thread-like processes; they have a sensitivity ("receptors") to stress and valium, and produce pregnenolone when activated. Under the influence of thyroid hormone, they wrap themselves in thin layers around the conductive parts of nerve cells, leaving a multilayered "myelin" coating. Their absorption of thyroid hormone is promoted by butyrate, an anti-stress substance found in butter and coconut oil.
Steroidogenesis is the creation of steroids, usually referring to the conversion of cholesterol to hormones.

Townsend Letter for Doctors & Patients.

By Ray Peat

Moles, DHEA, Etc.

Everyone knows what a mole is, but no one understands what a mole really is. Moles are interesting because they are simultaneously normal and a little abnormal. But it seems that no one has taken them seriously enough to study them very scientifically. At least, I don't know of any publications on "the epidemiology of moles," or "the experimental production of moles."

Advertisements from the cancer society fundraisers have taught people that "any change" in a mole could be a sign of cancer. The idea seems reasonable enough, but I think it has no clear scientific basis The fear of cancer has caused many people to have things excised as soon as they are noticed, but during this generation in which people have learned to have things cut out promptly, the incidence of melanoma has risen sharply. Melanoma first appears in normal- looking skin about as often as it does in pigmented moles, so the "preventive" removal of all moles is no guarantee that you won't get melanoma.

At least some pigment cells are "amoeboid," meaning that they can creep around. At body temperature, white blood cells under the microscope can walk about two inches per day.(1) These facts indicate that it could be seriously misleading to think of a bit of tissue, such as a mole, as a "strictly localized" thing, the removal of which has no meaning for the rest of the body.

I will just briefly mention some of the observations that have made me think of moles as "systemic phenomena."

A friend had many protuberant moles that had been present for most of her life (if not since birth), and one summer they withered, dried up, and fell off. She was taking a little more thyroid and triiodothyronine that summer.

One hot summer, I had a four ounce glass of Modelo beer, discovered I liked it, and for the rest of the summer I would often drink a similar small amount during he hot part of the day, while at my friend's house to water the plants. Two moles appeared on my forehead, and grew rapidly, until the bigger one was the size of a small pea. When the beer in the refrigerator was gone, the summer was nearly over, and I had thought increasingly about the estrogen content of beer, so I didn't drink any more. Within about a week, the moles were shrinking. The smaller one disappeared while the other one was still about the size of match-head. After about three weeks, the remaining mole was about the size of a dried pea, and one morning it rolled free when I touched it. It had become firm and dry.

DHEA Changes Moles

In 1980, a familiar old mole on my belly had begun growing and darkening. A couple of times when I had my shirt off on a hot day physician friends looked worried when they saw it and told me I'd better have it removed. It became thoroughly black, took on a sharply triangular shape, and had a firm leathery texture. By 1981, it was about 15mm. long, but still fairly flat. I had been experimenting with oral doses of DHEA in oil for two or three weeks, and had noticed that it made me feel like an adolescent, but it was causing me to get pimples.

One night as I was going to bed, I looked down and was shocked to see what looked like a maraschino cherry on my belly. I spontaneously flicked at it with my finger, thinking it might be an engorged tick, though the color and gloss weren't appropriate. Just before the second flick brushed it, I too late saw something black on the top of the globe, and realized that it was my mole. The black material brushed away, leaving a small drop of blood, but the dome remained glossy and red. By the next day, it was smaller and was no longer shiny from internal pressure. That afternoon I photographed it, and there was a red flare surrounding it, about 2

inches in diameter. By the third day, I could see that the deflating thing was going to be a brown mole, of roughly the same size as the original one that had been there a few years earlier. The only difference from its earlier state is that its margin might be more diffuse now.

In his mid-50s, my brother mentioned that he was getting a mole-like spot on his forehead. When I told him about my experience, and that I thought oral DHEA might have been responsible for the mole's disappearance, he applied a concentrated solution of DHEA in vitamin E directly onto the mole. A day or two later, he noticed a spot of blood on his pillow, and had his doctor cut the thing off, because of fear that bleeding signalled a malignant change.

After I found that a copper solution quickly caused my white eyebrows to return to their normal color, and repeated the experiment several times over about 3 years, I tried the same solution on my sideburns, and saw that some of those hairs had darkened after one application. It wasn't convenient to observe those hairs, so I decided to apply the solution to some white whiskers on my chin. After two or three applications, I carelessly used a solution that was too strong. Within less than a minute I felt it stinging, and washed it off. A stinging sensation was noticeable during

the next 2 or 3 hours, and I washed the spot thoroughly several times. About 4 hours later it was still a little uncomfortable, and when I looked at it in a mirror I was horrified to see what appeared to be a large, coffee-colored mole on my chin, in the area where I had applied the copper, and where the burning sensation persisted. The edges were slightly raised about the surrounding skin, and it looked li ke a normal light brown mole, roughly the size of a nickel. It was so hard for me to believe that such an anatomical change could have occurred within 4 hours that I wondered if I had just failed to observe something that had been developing gradually. But after about a week it had disappeared, and no trace of it has

returned, so I had to conclude that the high concentration of copper had acted with, or in place of, tyrosinase to form new pigment, or that copper-hungry cells had invaded the area.

A couple of years ago I noticed some moles on my upper chest were growing, darkening and developing an irregular, granular form. I hadn't used any DHEA for a few years, just because I had lost interest in it. A friend had just been telling me about using topical progesterone and DHEA in vitamins E and A to shrink a large and growing mole on her leg. For a few weeks I watched carefully as my moles changed since their location made it easy for me to view them at very close range. After becoming nearly black, I noticed that they were fading and becoming sort of grey. Then white and creamy areas appeared, and the grey seemed to concentrate into a few blue spots. The changes were surprisingly fast. I would look at them 2 or 3 times a day, and the blue, or black, or brown spots would be in entirely different locations each time. The moles had become firm to touch, but the spots of pigmented cells appeared to be swimming wildly around within the boundaries of the moles, as if looking f or something, or escaping from something. I smeared a very light film of vitamins A and E with DHEA over the area of my chest with the moles, and the next time I looked the color was becoming regular. Within a day or two, even the texture had returned to normal.

Higher Altitudes Decreases Cancer Incidence

About ten years ago, a cancer geographer mentioned that he had found an inverse relation between altitude and the incidence of cancer around the world. A woman from Texas who was at the conference was sure his information was wrong, because the higher intensity of "radiation" at high altitudes would increase the damage to DNA that is commonly supposed to cause cancer. She decided to disprove his work by doing a study limited to the incidence of melanoma - which is supposed to be especially sensitive to ultraviolet radiation - within Texas. Her results

surprised her; even melanoma incidence was lower at higher elevations.

Much of the doctrine about radiation at high altitude has been created by and for the nuclear industry. Actually, the dangerous secondary and tertiary particle showers from cosmic rays are more intense at sea-level than at high altitudes. But the greater oxygen pressure at sea-level might be the most important factor in various kinds of cancer, and other disease, since our antioxidant system can probably maintain better balance at high altitude. Mitochondria become more numerous at high altitude, and this might result from increased durability, as well as from the need for more efficient use of oxygen.

The skin is a major source of sterol formation. Skin changes in aging might indicate a special susceptibility to sterol deficiency, which could make topical application of steroid-associated materials especially appropriate.

About 50 years ago, melanosomes were believed to develop from mitochondria. Whether that was accurate or not, there are some interesting parallels between respiration and pigment metabolism. Copper, vitamin A, pregnenolone, progesterone, vitamin E and DHEA are intimately involved with both. The glucocorticoids tend to antagonize both.

Pigment Cells Related to Nerve Cells

Leghorn chickens are sometimes thought of as genetic albinos, but when relieved of the stress of egg laying, they can form black feather pigment. Domesticated animals of various kinds tend to become white. Soviet fox breeders selected foxes for tameness for 20 years. The foxes bred for tameness also lost their wild coloring, and became spotted.

The migration of pigment cells through the tissues of the developing embryo reflects in some way the altered balance of the whole organism. It is this distribution of cells during embryonic and fetal development, and later in life, which produces "birth marks" and moles. Pigment cells and nerve cells are closely related in embryonic development, so it is interesting to notice the similar appearance of astrocytes n the brain and melanocytes in the skin. Macrophages sometimes have a similar structure, and when stained with metals reticular macrophages and astrocytes (both have been called "metalophils") look surprisingly similar.

Metchnikov developed this theory of inflammation and immunity by phagocytosis in connection with his attempt to explain development, how ontogeny reflects - but alters - phylogeny. The recognition and preservation of self, in the immune reactions, was just an aspect of the ontogenetic creation of individuality.

When my phagocytes eat up one of my moles, and a good copy of my "original" mole is reconstituted in the same location, Metchnikov's idea of a dynamic organismic integrity, in which the phagocytes play a central developmental role, takes on new concreteness for me.

In 1983 I noticed that the whiskers on my cheeks were going white in circular as if the melanocytes were migrating centrifugally. Around the same time I noticed a flat mole, or raised freckle, was growing on my temple. Although many people have those spots removed, it is very common for people in their 80s to have a button-like black spot on the temple. My spot waxed and waned, but on average tended to get bigger and darker with the years.

In Mexico recently, a friend found that applying DHEA in vitamin E to a very big, red keloid tumor caused it to quickly fade and shrink. As I was driving home, I applied a little of the same solution to one of the mole on my temple. A day or two later I

noticed a concentric ring of brown skin on the opposite side of the mole, about a centimeter away. The next day, there were two such bands. Then a bright red line appeared at the front margin of the mole, where I had first applied the oil. Although it looked as though the edge of the mole had bled, it was actually just a thread-like region of extremely dilated capillaries. Day by day, the thread of red appeared to be

contracting around the mole. The brown rings took on a V-shape, and extended into the hair. The color of the mole became lighter for about a week, and as the red thread "contracted" the flat mole became pedunculated and mostly colorless, like a tiny mushroom. Two or three dots of color remained, apparently trapped, in the globe. After drying and shrinking for a couple of days, it fell off, and the point of attachment had become smooth, normal skin within a day.

In this case, the concentric rings of brown pigment suggested that pigment cells might be returning to their normal locations, after having lived for ten years in an island on my temple. This might suggest that this particular skin area is the last to lose its ability to produce DHEA, and that well-nourished cells can remember where they belong.

Lipofuscin Produced in Oxygen Deprivation

Age pigment, lipofuscin, is produced in oxygen deprivation, apparently from reduced iron which attacks unsaturated fats. It has its own "respiratory" activity, acting as an NADH-oxidase. Melanin is produced by polymerization of amino acids, with copper as the catalyst. With aging, iron tends to replace copper. Melanin is an antioxidant. Thus, there is a sort of reciprocal relationship between the two types of pigment. A vitamin E deficiency relative to consumption of polyunsaturated fats, and an estrogen excess, accelerate the formation of lipofuscin.

A 47 year-old woman who had only a few "liver spots" on the backs of her hands began taking large amounts of estrogen, and within a few months the brown spots had darkened and spread until most of her skin was covered with spots. When she stopped using estrogen, and applied progesterone topically, the spots disappeared.

Since both keratinocytes ("keratinophages") and "melanophages" can phagocytize melanin granules,(2) the occasional rapid disappearance of "age pigment" makes me wonder whether pigment-loving cells can't ingest and destroy lipofuscin. To the extent that lipofuscin wastes oxygen, the phagocytes might be able to relieve some of the symptoms of oxygen deficiency in aging. (My recent experience with an 82 year-old man with emphysema who regained a normal pink color a few days after beginning to use DHEA and pregnenolone led me to wonder whether the improvement was mainly in the lungs, or in the other tissues.)

If leukocytes can direct organized attacks on moles, with reconstruction of healthier tissue at the same location, the healing of an infection, or a wound, should be seen in the context of growth, construction, and creation, instead of simply attack upon a foreign body.

If leukocytes remove age pigments and deteriorated moles by recognition of an "age antigen," as in their removal of old red blood cells, or the unnecessary tadpole tail in maturing frogs, then we have a way to begin to grasp the mechanism of ontogenic evolution through various stages and "recapitulations of phylogeny," rejecting one structure as another step forward becomes possible. (The fact that the senescence antigen appears in embryonic kidney cells, as well as in adult liver cells, indicates that it has to do with development, the transition from one stage to another, rather than simply with the "wearing out" of cells.)

Melanoma sometimes spontaneously regresses, in a self-digesting manner.(3) This might be the process that I have seen in my "autolytic" moles. The fact that the "tumor necrosis factor" is also a cachexia inducing factor (and is produced by activated macrophages) provides another perspective on the idea that the whole body might be designed to periodically melt-down, to be systematically reconstructed anew.

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~~~~~~~~ By Raymond Peat
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Mortality Again

by Ray Peat, Ph.D.
Ray Peat's Newsletter

Maria de Sousa's work on thymus-derived cells and their relation to the body's iron economy has made people aware of the possibility that iron "fortified" flour and other foods might be contributing to the incidence of leukemia and other cancers, and to immunodeficiency resulting from maldistribution of lymphocytes.

"And with the weight of iron advertisements in this country one inevitably starts feeling that it is not going to be easy to tell this community that in some circumstances iron may be bad.

"It is iron and flintstones, and the food almost all of our Hodgkin's children ate – as we found out from the rough survey of eating, drinking, and living habits." (June Goodfield, *An Imagined World,* 1981).

It was probably the World Health Organization's observation of a high death rate from malaria in people who were given supplementary iron for their "anemia" that made it obvious that iron can have rapid and deadly immunosuppressive effects, though it had long been suspected that an increase in the iron burden was a factor in the immunosuppressive action of blood transfusions. My interest in the toxicity of iron was aroused by the published discovery that, when added to animal food, iron destroys the vitamin E which was also added to the food. Subsequently, it was found to destroy other vitamins, too.

In recent years, the interaction of iron with vitamin C (and other reductants) and unsaturated fats, to produce lipid peroxidation, has been the dominant issue in research on the toxic effects of iron. "Reperfusion injury," any stress causing oxygen depletion and an excessively reduced (electron-rich) cellular state, the importance of lipid peroxidation and iron in aging, and the role of iron in damaging steroid synthesis in steroidogenic tissues, have been important lines of study lately.

Early in the century, the tendency of calcium and iron to be deposited together in damaged tissues was noted, but the exact reason for this association still isn't known. I think iron's role in "age pigment," lipofuscin, is an important part of the mechanism. In oxygen deprivation, heme (the iron-binding oily component of hemoglobin and various enzymes) is produced, largely by spontaneous, non-enzymic means. Age pigment consists mainly of lipid peroxidation products, with heme and iron. It has the adaptive function of keeping NADH oxidized in a low-oxygen environment, in which mitochondrial respiration is inadequate, allowing NADH to keep the glycolytic sequence operating. It has been found that age pigment is produced in the fetus, because of its low-oxygen environment, and in fish that are living under ice, again because of the low-oxygen environment, which allows iron to become reduced and to catalyze lipid peroxidation. In old age, blood leaving the lungs is often only half saturated with oxygen; the tissues are likely to be overloaded with iron, and it becomes increasingly likely that fat will be mobilized as an energy source.

The other factors besides iron overload and oxygen deprivation which cause premature loading of the tissues with "age pigment" are a diet low in vitamin E and/or high in unsaturated fats, and an excess of estrogen.

Around the time these factors in the formation of age pigment were being investigated, the Shutes were investigating the antagonism between estrogen and vitamin E. Essentially, their antagonism consists of the fact that vitamin E spares oxygen, and that estrogen wastes oxygen.

Women absorb dietary iron about three times as well as men do, but during pregnancy their absorption is about nine times as efficient as men's.

The famous antagonism of molybdenum to copper absorption is similar to that between iron and copper. Copper deficient cells, for example in the heart, become overloaded with iron. Recently, various studies[1] show that cellular oxidative stress promotes iron retention, which would be logical, since iron is essential for respiration, and cells struggling to respire would tend to use evolved mechanisms for retaining the iron needed to form new respiratory enzymes. (As I suggested above, I think spontaneously formed heme is the probable reason for iron's tendency to concentrate in hypoxic tissue.) Estrogen, by creating relative hypoxia, promotes iron retention.

The fetus, a whole organism within an organism, has a special oxygen problem. Fetal hemoglobin, with a great affinity for oxygen, helps it survive in that situation. (I suspect that fetal hemoglobin will reappear whenever there is prolonged hypoxia.)

I believe it is the low oxygen environment which causes the fetus to be born with a great surplus of iron. Prenatally, iron is absorbed about 40 times faster than while

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the baby is nursing. Although pregnant women absorb iron from food very efficiently, they tend to give up their stored iron to the baby. This could account for the greater longevity associated with having more babies, and especially with the lower incidence of cancer in child-bearing women.

Milk is remarkably "deficient" in iron, and it seems obvious that this is an adaptive feature, allowing the child to "grow into" the large amount of iron stored in its tissues at birth. I mentioned the fact that iron and calcium both tend to be deposited in damaged and dying tissues. If it is the situational hypoxia of the fetus that causes its prenatal iron overload, we might expect it to be "overloaded" with calcium, too, and that seems to be the case, with the extra calcium being stored in the porous centers of the bones.

Estrogen causes an exaggerated absorption of calcium, as it does of iron, and high calcium diets have been found to be very toxic to pregnant animals. The combination of estrogen and calcium can cause a condition called osteopetrosis, or hardening of the bones, in which the bone-marrow cavity is closed up, severely limiting the production of the cells which would become Natural Killer cells, normally found in the spleen. Estrogen causes a reduction of Natural Killer cells in the spleen, even without destruction of the bone marrow.[2,3]

Estrogen, and a variety of poisons, cause even soft tissues to retain calcium. It is clear that scleroderma, a hardening of the skin, involves the interaction of calcium, iron, lipid peroxidation, and hormones, but lately it seems that no one wants to think about it physiologically. The food and drug industries have their motives; we are hearing more about drugs to chelate iron and calcium from the body, than about simply leaving iron out of food, or restoring vitamin E and magnesium. And researchers like to aggrandize themselves by making problems seem more complex than they really are. And of course, disease-centered fund-raising organizations always see their business as raising funds, not finding cheap solutions to problems.

At the age of 12, people are less likely to die than at any other age. The curves for mortality from cancer, and from all causes combined, are similarly shaped, with a minimum around the age of 12. The sex hormones tend to stop bone growth, at least in the sense that puberty leads to the hardening of the growth-areas of long bones. When growth stops, the concentration of iron in the tissues tends to increase (even without considering the effect of hormones on iron absorption).

The high mortality of old age is associated with a high concentration of iron in the tissues, just as the high mortality of young infants is associated with a high concentration of iron. As the infant's iron is diluted by growth, mortality decreases.

Infectious disease and leukemia, which have been associated with excess iron, are highest in childhood and old age.

June Goodfield's book gives a nice summing up of the early research on the relation of iron metabolism to cancer and immunodeficiency:

"...in essence the immunological system has evolved with the ability to survey, and recognize, and utilize – I don't know exactly what. But this ability is expressed as a capacity to survey metals and, in particular, iron.

"It goes in as ferrous iron, and is then rapidly oxidized into ferric iron. This is then bound to a protein, transferrin, and so is carried into the bone marrow and thus given to the early red blood cells, which need it for the blood cycles. But iron is also bound to a second protein, ferritin, which is a storage protein.... When red cells get old they break down in the spleen and are eaten up by the macrophages, which then make ferritin. (It enters the storage pool again.) Then there is the third protein, lactoferrin, which is synthesized by polymorphs, the white cells, and is present in milk and in our secretions. The amount we excrete per day is absolutely minimal. You can only shove it in; you can't push it out. Now if, for some reason or other, there is too much iron around, the macrophages go and mop it up. And as far as I'm concerned, in the diseases we've been studying – Hodgkin's, leukemias – there is an abnormality in the lymph nodes and the macrophages in regard to the intake, or the handling, of the iron. ...I have a simple scheme, again probably too simple. Lymphocytes go and are caught where there is an excess of iron. A malignant cell, like a virulent cell, behaves like a virulent bacterium. It becomes capable of sucking up iron avidly and utilizing it. ...if the tumor cells eat up the signal – iron – the lymphocytes won't go there. The tumor will grow undisturbed because the lymphocytes have not had a signal to move toward it."

As I mentioned above, I think some of the excess iron accumulates in the form of age-pigment, and that this material serves to keep glycolysis running as an emergency energy source. Glycolysis produces lactic acid, which is characteristic of tumor metabolism even in the presence of oxygen, and lactic acid has its own direct effects on immunity.

Americans who eat processed grain products are obliged to eat iron, because of the federal law that they must be "fortified," in spite of the clear evidence that adding iron to food destroys its vitamins. Only public pressure can change this law. Those who have promoted the use of iron fear change, because of their potential liability.

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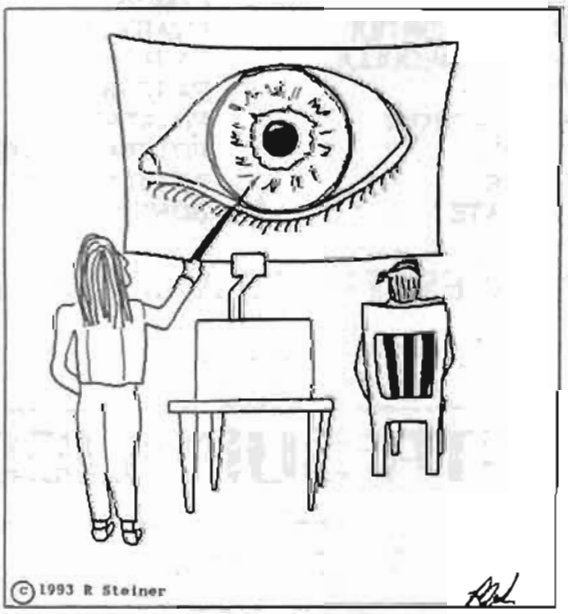
THE LIGHTER SIDE OF IRIDOLOGY...



Here's mud in your eye.

Letters to the Editor

Diagnosing Porphyria for Labor and Industries Claims

Editor:

Polycythemia, scleroderma, and porphyria have several elements in common, but I have never seen a discussion of this. Although I have written about them before, my articles on these subjects haven't been widely published. When I saw all of these topics mentioned on the same page of the *Townsend Letter* (February/March 1996, page 98), it seemed that I should point out some of the features that make these a sort of family of disorders.

These are disorders of tissue respiration and energy production. Oxygen, estrogen, and iron have important roles in all of them. Men are more likely to have polycythemia, women are more likely to have scleroderma and some types of porphyria.

The Washington State Department of Labor and Industries' review of porphyria is representative of a bureaucratic approach to a disease in its exclusion of all of the publications that offer an opportunity to understand its mechanism in a general way; I think it is setting the stage for a pro-industry/anti-worker policy, in drawing its distinction between problems "triggered by" exogenous chemicals, and those "potentially *caused* by an exogenous chemical exposure." Scientifically, this sort of categorization is meaningless. I think it is reasonable to interpret any increase in porphyrin metabolism as possible evidence of work-related damage, which compromises the worker's adaptive capacity in many ways.

The document at one point approaches a recognition of the silliness of their approach: "It can be argued semantically that this was not a true 'porphyria,' because of the absence of hereditary enzyme deficiency; however, there is little question that this acquired 'porphyria-like' condition was highly morbid and also clinically indistinguishable from the inherited form of porphyria cutanea tarda."

Until the doctrine of significant genetic causation is subjected to the requirement of being obtained in *"a rigorously designed, blinded and appropriately controlled manner,"* it would have to be considered *"speculative and unestablished,"* if this document were coherent. (It appears that its authors drew their gun intending to cripple a branch of alternative medicine, and shot their argument in the head.) The document's emphasis on defining the disease in terms of genetic deficiency gives the enterprise an overwhelmingly anecdotal quality, at best. Let us see the rigorous evidence on which the categorization is based.

The document bases its whole presentation on the presumed reality of "hereditary *deficiency*" of enzymes, and – probably for a reason – ignores the evidence for an enzyme *excess*, which can be so easily induced chemically or hormonally. Early steps in the prophyrin synthetic pathway are influenced by the availability of precursor substances and by the concentration of heme, and are extremely susceptible to environmental influences. The issue of the role of genes in the balance and organization of a complex enzyme system is so tenuous that the citizens of Washington should look into the state's manner of choosing its experts.

There is a long history of investigating the interactions of porphyria metabolism with estrogen (L.C. Strong, Sex differences in pigment content of Harderian glands of mice, *Proc. Soc. Exp. Biol. Med.* 60, 1223-125, 1942), with cancer (e.g. F.H.J. Figge, et al., *Cancer Res.* 2, 335-342, 1942), with diet, and with excess iron. Estrogens are known to cause porphyria (R.D. Levere, *Blood* 28, 569-572, 1966), and to exacerbate the symptoms and biochemical disturbances in people with subclinical porphyria. Sometimes symptoms occur premenstrually, during the time of increased estrogen production – the term "ovulocyclic porphyria" has been in use for a long time. Puberty therefore increases the susceptibility to symptomatic episodes.

Porphyria synthesis begins at an important cross-over point of protein and carbohydrate metabolism. Succinyl CoA and amino levulinic acid can enter the Krebs cycle or the porphyria pathway. Protein catabolism feeds into these pathways. Increased protein catabolism or blockage of oxidative consumption of Krebs cycle fuel – for example by poisoning – makes these precursors available to enter the prophyrin pathway. Stress-induced oxidation of heme can eliminate feedback control, but the specific outcome can be modified in many ways.

Many serious long-range consequence of excess heme/porphyrin production and metabolism are currently being investigated, suggesting that a criterion of "twice the upper limit of normal" excretion, for recognizing that a problem exists, could allow far more serious problems to develop over time, that on the surface might seem unrelated to porphyria. In some cases of porphyria cutanea tarda, scleroderma-like hardening of skin occurs, but the ramifications of disturbed heme metabolism, resulting from exogenous factors, are far-reaching. For example, G.Y. Kennedy, at the Cancer Research Laboratory, University of Sheffield, observed that a porphyrin shortened the time required to induce tumors, and porphyrin derivatives have been proposed to be "cancer hormones." The carbon monoxide produced in the breakdown of heme inhibits many enzymes.

The synthesis of heme/porphyrin, and the production of red blood cells, are stimulated by a lack of oxygen, or by toxins such as arsenic and iron, which cause oxidative stress. Emphysema, high elevation, sluggish circulation, and nocturnal breathing problems can cause enough oxygen deficiency to stimulate the formation of new red blood cells. Newborn babies often have polycythemia, as a result of limited prenatal oxygen supply. At a certain point, the continued production of red blood cells can make the blood so viscous that this viscosity impairs circulation through capillaries, and creates a vicious circle, stimulating the formation of more red blood cells. Men are more likely than women to have polycythemia rubra vera, possibly because testosterone is anabolic to the bone marrow, and estrogen tends to slow blood cell formation (females of all species are relatively "anemic," compared to males, partly because their blood is more dilute), but I think the greater ability of men's marrow to respond proliferatively to hypoxia is influenced by many factors, including different nutritional requirements. (Estrogen tends to cause certain vitamin deficiencies and fluid retention.) Estrogen also significantly lowers body temperature, while testosterone tends to raise it, and the temperature of the bones is a powerful factor in forming new blood cells. But this isn't to suggest that the patient could benefit from increased estrogen, because

estrogen consistently lowers the availability of oxygen.

Excess estrogen reduces the blood's oxygenation, for example by producing a barrier to oxygen diffusion in the lung. Hypothyroidism (which is causally related to an excess of estrogen) is known to predispose to emphysema, and treatment with thyroid hormone has often cured polycythemia vera, presumably by improving respiratory efficiency. Progesterone, which is known to stimulate the brain's respiratory control system, has also been used successfully to treat polycythemia, and in animal studies it corrects experimentally induced emphysema. These treatments for polycythemia vera were mentioned about 30 years ago (in *JAMA*, I think, though I don't mention that to give the observations credibility, just to show how generally distributed the information has been). In Colorado, where the incidence of polycythemia is high, it was found that teaching men to get in the habit of breathing more deeply could solve the problem.

Although there has been a medical faction that liked to compare polycythemia with leukemia, to justify treatment with radiation or cytotoxic/carcinogenic chemotherapy (and following the treatment, the patients did get leukemia, confirming the doctors' belief in the connection between the two diseases), simply removing some blood and replacing it with fluid to bring the volume of red cells down to 45 to 50% improves exercise performance in polycythemia patients with chronic bronchitis, emphysema, overinflated lungs and hypoxia (B.D.W. Harrison, et al., *Clin. Sci.* 45, 833-847, 1973). H.P. Ward, et al. (*Am. J. Med.* 45, 880-888, 1968) found that in some patients, lying down or sleeping could cause enough oxygen deficiency to increase red blood cell formation. Increased viscosity of blood, and increased levels of adrenalin produced in response to hypoxia, cause increased risk of excessive blood clotting and thrombosis.

In my experience, clinical emphysema responds very well to pregnenolone, and for men, this has advantages over both progesterone and thyroid.

Impaired lung function is very common in scleroderma, even when there seems to be no evidence of lung involvement (C.T. Huang and H.A. Lyons, *Am. Rev. Resp. Dis.* 93, 865-875, 1966).

Metal poisoning is often mentioned as a cause of both porphyria and scleroderma. It was probably this medical association that caused Hans Selye to create the animal model, in which the injection of iron contributed to the development of scleroderma. (H. Selye, *J. Invest. Derm.* 39, 259, 1962; Selye and B. Tuchweber, *Quart. J. Exper. Physiol.* 50, 196, 1965.) Injected iron damages the liver (J.A. Nissim. The entry of iron into liver parenchyma cells following injection of different iron preparations, and the different lesions produced with toxic doses, *J. of Physiology* 117, 66-67, 1952), and practically any kind of liver damage leads to estrogen excess and a chronic stress-like adaptive response.

Scleroderma used to be described as one of the "collagen diseases," because similar changes in blood vessels and connective tissues were seen in systemic lupus erythematosus, rheumatoid arthritis, polyarteritis, drug hypersensitivity, etc. (G.P. Rodnan; Progressive systemic sclerosis (scleroderma), in J.I. Hollander and D.J. McCarty, Jr., editors, *Arthritis and Allied Conditions*, Lea & Febiger, 1972). Scleroderma (similar to several other "autoimmune" diseases) is much more common in women than in men, and animal models for several autoimmune diseases can be produced with estrogen treatment. Scleroderma often begins with edema of the extremities, Raynaud's phenomenon, and muscle weakness or "polymyositis," which are commonly seen in hypothyroidism/hyperestrogenism.

It is generally agreed that collagen is overproduced in scleroderma, and there is evidence of increased mucopolysaccharides in the skin (O. Braun-Falco, *Derm. Wschr.* 136, 1085, 1957). This is reminiscent of hypothyroid myxedema; it has been suggested that mucopolysaccharides can act as a matrix for calcification (W.C. Johnson, et al., *J. Invest. Derm.* 43, 453, 1964). Estrogen stimulates the formation of collagen, and increases its age-like properties, and progesterone opposes some of these pro-aging effects on connective tissues. Mere lack of oxygen stimulates collagen formation, and the opposing effects of estrogen and progesterone on tissue oxygenation can account for many of the tissue changes they produce.

Oxygen deprivation causes tissues to retain calcium (and iron), as does estrogen in many cases, being similar to aging in promoting cellular uptake of calcium. Since the porphyrins strongly bind metals, it has been suggested that they may have a role in mediating the deposition of metals in stressed tissues. Paroxysmal vasospasm occurs in about 90% of scleroderma patients, and estrogen and adrenalin are known to synergize in producing vascular spasm; hypothyroidism normally involves elevations of both estrogen and adrenalin.

More Letters

I have known women who developed scleroderma after beginning the use of estrogen, and who are reluctant to stop, because they had been told that estrogen would protect them from osteoporosis and heart disease. Men who have had a diagnosis of scleroderma have told me that with the use of thyroid and magnesium supplements, Epsom salts baths, and topical progesterone and vitamin E, their symptoms regressed.

Polymyositis sometimes leads to calcification, and this would be expected if the problem is related to mitochondrial respiration, as is now generally thought to be the case; thyroid and magnesium are often the factors needed to normalize mitochondria and prevent calcification.

Tumoral calcinosis is sometimes treated as a variant of scleroderma, but it is very different, and tends to be localized, without internal complications. I think many people get minor bony excrescences (bone spurs, osteophytes, exostoses, hyperostoses) during puberty, or at other times of hormone imbalance, which often disappear spontaneously, but this probably represents the same basic process, and would have very little to do with the severe oxygen deficiency states in which collagen synthesis is overstimulated. Growth hormone and prolactin imbalances have been suspected to have a role in some of these growths. (Both of these pituitary hormones are elevated by estrogen, and hypothyroidism is often the cause.) Progesterone, thyroid, bromocriptine, and other things are available to normalize the pituitary, when that is responsible.

A weakened ability to oxidatively produce energy can lead to the maladaptive over-production of collagen, porphyrins, and red blood cells. Considered together, I think the mechanisms involved in these diseases argue for the importance of the nutritional-environmental approach to health care. The medical/bureaucratic preference for a "genetic" rationale for disease has overtones of "eugenics." When the state gets involved in genetics, eugenics, or medicine, they had better keep their own scientific standards at least as high as those they demand of the people they disagree with.

Ray Peat, Ph.D.
Ray Peat's Newsletter
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Letters to the Editor

Re: Ray Peat's View of *Fats & Oils*

Editor:

I wrote the book: *Fats and Oils: The Complete Guide to Fats and Oils in Health and Nutrition* (1986), published by Alive Books, 4728 Byrne Rd., Burnaby, BC, Canada V5T 3H7. $27.50 in hardcover; $16.50 in softcover.

Ray Peat's accusation that *Fats and Oils* is an "error-filled, incompetent and possibly deliberately misleading" book surprised me. His letter requires detailed correction.

1. Ray Peat suggests that I might be "a hired commercial writer working from information provided by his employer." Wrong.

In fact, I buried my head in the journals for 3 years part-time and 3 more years full-time to gather the information presented in the book. I began because I had a health problem for which I could find no medical solution. Studying nutrition, I noticed that fats and oils play a part in many degenerative conditions. I wanted to get to the bottom of that and did.

2. He says: "I suspect that neither Erasmus nor Budwig has studied the fundamentals of organic chemistry." Wrong again.

I studied the fundamentals of organic chemistry, as well as several courses in biochemistry, a graduate course in the biochemistry of lipids among them, at the University of British Columbia. With 6 years of university studies in the life sciences, I continued studies on my own.

Budwig's understanding of organic chemistry and biochemistry is impeccable. She authored several papers published in reputable German lipids research journals and a dozen books. Extremely innovative, she has used her expertise to attain brilliant insights into product development from the point of view of human health.

3. He claims that I recommend "linoleic acid, and related oils, in...amounts known to cause serious health problems," which he lists.

I make a distinction between what I report (from research and clinical findings) and what I recommend (based on what I understand about health). I have only recommended one oil: *fresh flax seed oil* (which is high in the omega-3 alpha-linolenic acid and low in omega-6 linoleic acid).

Made by a company called Omega Nutrition, the flax seed oil that I have recommended is mechanically pressed from certified organic flax seeds by an especially painstaking light-free, oxygen-free, low temperature method (OMEGAFLO). The oil is unrefined, packaged in completely opaque containers (to prevent destruction by light), dated with a 4 month shelflife, and shipped refrigerated.

I have recommended this oil because it sets a precedent and a new direction in the manufacture of oils. If human health is really our concern, this is how, in my opinion, oils need to be made. In *Fats and Oils*, I devoted 2 chapters to making and labeling "healthy" oils. Omega Nutrition exceeded all of my specifications. I have no legal or financial affiliation with the company, and do not profit from their sales.

4. I distinguish between *linseed oil* and *flax seed oil*. Linseed oil is the name used in the industry for paint-grade oil, pressed from flax seeds without the care that human consumption requires. Linseed oil is considered inedible, but finds its way into our food supply nevertheless, both in bottles and in capsules.

Flax seed oil, on the other hand, is the name we give to oil made with the care required for human health, marketed fresh, refrigerated, and hopefully shipped direct to the retailer or consumer.

I do not recommend any brands of oil called linseed (flax) or flax (linseed). After only 2 years of production, there are already several imitations on the market, none of which I recommend. Quality and greed carry us in different directions.

The flax growers like a distinction to be made between the paint-grade and the human-health product, because they, too, don't want the confusion of terms and products.

5. From the health point of view, I do not recommend *any* refined oils (because of destructive processing and removal of nutrients), *any* non-organic, unrefined oils (because of pesticide residues), or *any* oils packaged in transparent plastic containers. One could hardly call me a friend of the billion-dollar oil industry.

6. I recommend a total of 15 to 20% of calories from fats in the diet of most people. This is 10% lower than the recommendation of the American Heart Association, but in line with traditional diets not leading to cardiovascular disease. If 2% of daily calories were omega 3's, 4% omega 6's (I suggested 3 to 10% in *Fats and Oils*), 5% mono's and 5% saturates, they might constitute reasonable ratios for health. The body adapts to fluctuations in the ratios. It cannot handle too many saturates or too many omega 6's. It needs both essential fatty acids. A balance is prudent.

Pritikin's diet, in my opinion, was too low in total fats, too low in omega 3's, and too low in vitamin E. His diet is useful in the treatment of obesity and atherosclerosis, under supervision. It fails as a way of life for healthy people.

I strongly disagree with the "fat is poison" sentiment. There is too much research evidence for the essentiality of fats and of essential fatty acids in the diet. Too little or too much results in problems.

7. I agree that an excess of the omega-6 linoleic acid, especially from refined oils, fried omega-6 oils, and an omega-6 containing diet lacking antioxidants leads to health problems. I consider this now established fact important enough to emphasize in every lecture I give.

8. My apologies to Dr. Jeffrey Bland, for being misquoted. The quote in Peat's letter was taken, not from the book's introduction which *was* written by Dr. Bland, but from an advertising flyer assembled by the publisher of *Fats and Oils*. In all of my dealings with Dr. Bland, I have found him to be conscientious, detailed and accurate. I have no reason to believe that he acted contrary in reviewing the manuscript of *Fats and Oils*.

9. Dr. Max Gerson *did* use fresh flax seed oil in his work. He called it linseed oil (unfortunately, in my opinion). The Gerson clinic, operated by his daughter, uses Omega Nutrition's flax seed oil, with good results in the treatment of many degenerative diseases.

The telephone number of the Gerson Institute, where one can obtain more information about Dr. Gerson's methods is 619-267-1150. I prefer to let them tell the story of how Dr. Gerson came to include the oil in his treatment, and what results he had then and now.

10. I have never met Mike Minarsich. He is not a scientist, but a promoter. He, like many others since the book came out, has eagerly quoted me to sell his particular brand of products. He has done so without my permission. I in no way endorse or recommend his products.

11. I am a writer and educator, doing my best to spread the word about fats and oils, cholesterol, essential fatty acids, omega 3's, human health and natural therapies. I earn my living by charging fees for education and consultations, and collecting royalties on books.

12. Finally, a word about oxidation and anti-oxidants. In the last few years, we have given anti-oxidants a lot of deserved attention. In the process however, we have almost forgotten that animal and human life *depend* on oxidation. Oxidation produces energy. Lack of oxidation results in lowered metabolic rate, lower energy levels, and degeneration.

The essential fatty acids (especially the omega 3 essential fatty acid alpha-linolenic acid) constitute the highest level oxidants in human nutrition. We require them for our oxidation-dependent life.

In the final analysis, the energy which keeps us alive is generated by a finely regulated balance of oxidation and reduction, by a proper balance of oxidants and anti-oxidants. The fats and oils, in their natural form, are a necessary part of this balance.

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Another in Response to Ray Peat

Editor:

It is with great interest that I watch the criticism and rebuttals that occur issue to issue. After reading Raymond Peat's opinion, footnoted only by his own newsletter, I must step into the battlefield.

Our company Omega Nutrition supplies fresh flax oil to several of the fatty acid researchers in the world. If Mr. Peat would read some of the orthodox medical journals listed below such as the *JNCI*, *Lancet*, *JAOCS*, he would see just how misinformed he is.

Mr. Peat's article mentions linoleic acid as causing problems ranging from brain impairment to suppressed immunity. The point Mr. Peat has missed is that Flax oil contains only small amounts of linoleic acid. Flax oil is predominantly *linolenic* acid, a substance proven to be essential in brain development and learning, slowing aging and age pigment accumulation, repairing damage to the circulatory system, selectively kills certain cancer cells, increasing immune response, coincidently all the things Mr. Peat has claimed contrary.

It appears Mr. Peat has got linolenic acid (Omega 3) confused with linoleic acid (Omega 6). Linoleic acid (common in most oils) is definitely involved in promotion of cancer due to lack of production of cyclooxygenases and increased PGE 2 production. Omega 3 fatty acids can control PGE 2 production to some extent. Dr. Karmali found the best ratio of Omega 6/3 is 1/1 for preventing cancer and that Omega 3 works by preventing immunosuppression of cell-mediated immunity. Flax oil typically contains 55-60% Omega 3.

It disappoints me that a person does not make a reasonable attempt to understand a subject before he criticizes something and that he footnotes his entire article from his own newsletter. When one bases his whole criticism on an excerpt from his own newsletter, one can conclude that Mr. Peat is on a subscription drive.

I have attached several reputable references and research facilities supporting the above facts. Our company has received letters from people who have been given up by the medical establishment, but have been greatly helped by using our flax seed oil. The only side effect we have had reported is from people who have severe liver problems and have problems digesting *any* fat.

I applaud the *Townsend Letter* for allowing the wide arena of letters to the editor so information and discussion can be publicly aired.

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AJCN, #44, Sept. 1986, page 336-340; Linolenic Acid and Blood Pressure

Nutrition Today, Mar to June 1988, pages 10-19, 12-18

Lancet, Vol 2, Nov. 7 1964

JAOCS, Vol 65, #4, April 1988, Page 509

Prostaglandin Leukotrienes & Medicine, 1985, Pages 177-186

SA Medical Journal, Vol 62, Oct 1988 page 500 and Oct 30 1982 page 63

Current Research in Progress

USDA, Dr. Levander, Beltsville, MD Treatment of Malaria

Dr. Cunnane, U of Toronto, Diabetes

Dr. McDonald, U of Manitoba, Reducing Cholesterol

Pierre Budowski, Israel, Linolenic acid slowing down and reversing aging making cell walls and membranes more flexing.

Dr. Martha Neuring, Oregon, Linolenic acid necessary for brain development and learning disabilities.

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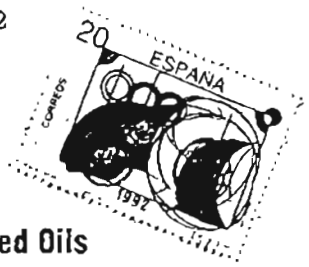

Cold Pressed Oils

Editor:

Rheumatoid arthritis is presumed to be an autoimmune disease, at least it is an inflammatory disease. In the January 26, 1985 issue of *Lancet* Kremer et al. spell this out. Then they use MAX EPA to suppress inflammatory action, in other words to be immunosuppressive. Here they were using a fish oil product that could be expected to be all cis isomers and no trans isomers. In *Lancet* for March 18, 1978, Bower and Newsholme used 30 ml. of sunflower seed oil which most likely had about 5% trans isomers and 95% cis isomers, and 0.5 ml. of wheat germ oil which would be all cis isomers. The oil mixture used here had to be highly immunosuppressive to have an effect on an autoimmune disease such as the Guillain-Barre syndrome.

Now a bit about cold pressed oils. I rather doubt if there are any on the market today, even though they are sold as such. The presumed benefit of cold pressed oils is that they would be free from the harmful trans isomers.

Trans isomers of PUFAs were never in human food prior to about 1925. They are formed in the caustic refining of vegetable oils and in far greater amounts by the hydrogenation process.

I know a great lot about flax seed oil and I will tell some of it here. From Berlin east across Poland and Russia before about 1930, small food stores had presses for the pressing of flax seed oil. On pressing flax seed about 40% of the oil was removed. The customer would be given the oil and the press cake which contained the other 60% of the oil. This press cake would be taken home and used in making black bread. The flax seed cake was what made bread black. Newly pressed flax seed oil has a pleasant nutty aroma. Let freshly pressed oil set on the shelf for a week or so and brown phosphatides will settle out at the bottom of the bottle.

I do not know how much oil one can get by pressing soya beans, but the oil one would get would have a most unpleasant and disagreeable odor. Also, as soya oil is higher in phosphatides, there would be about 3 times as much brown sludge settle out. Refined, this sludge is soya lecithin.

I see nothing even remotely like what I have described here, being sold in health food stores as cold pressed oil. I suspect that what is being sold is refined oil, sold under a false label. By the by, with the exception of flax and olive oils, most crude oils have an unpleasant aroma and it is for that reason that they are refined.

There is nothing wrong with hexane extraction of vegetable oils. I feel certain that Vioben Laboratories hexane extracts its wheat germ oil. With Efamol Research, they are keeping a secret how they extract evening primrose oil, but I would bet a lot that it is hexane extracted. Fresh hexane extracted soya oil smells awful, however it is free from trans isomers.

If one wants some PUFAs free from trans isomers one should eat food containing them such as walnuts which are 50% oil by weight.

Wayne Martin
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Are We Guilty of Candida Overkill?

Editor:

A recent interview with Dr. David Soll, Professor of Biology at the University of Iowa, suggested that systemic Candida infection as described in popular books such as *The Yeast Connection* is highly unlikely to be the cause of the chronic fatigue syndrome.

Dr. Soll's research indicates that Candida albicans possesses a high frequency switching system that allows it to make rapid changes in its physiology, anatomical shape, cell wall antigens and hence, its resistance to the immune system of the host and common antifungal drugs. Soll claims that nearly 100% of candidiasis cases diagnosed by questionnaires alone show negative cultures. Additionally, he claims that there is no evidence to prove that Nystatin or other antifungal drugs cure the syndrome. Consequently, it is his opinion that a large number of patients are being treated unnecessarily for symptoms that may be caused by other, more serious medical problems.

In an effort to assess the validity of Dr. Soll's findings, I selected 61 cases of patients from my practice who presented complaining of chronic fatigue and had the following characteristics:

1) A score of 200 or higher on the Crook questionnaire.

2) Cultures done for Candida on at least 3 different body secretions or mucous membranes (stool, buccal, pharyngeal, nasal, vaginal).

3) Antibody (IgG, M,A), antigen and immune complex titers done for Candida.

4) Inhibition of lymphocyte blastogenesis and NK cell activity by Candida test done (Wojdani Stage 2 Candida test technique).

5) Had already had more serious medical diagnoses ruled out by either internists or other specialists.

Table 1 shows the patients with the high Crook questionnaire scores, the results of their cultures, antibody levels, Stage 2 test results, whether they were treated for Candida or not and the presence of other diagnoses.

Table 2 indicates that of the 61 cases with positive Crook questionnaires, 24 (39%) had a positive culture and 25 (41%) a positive Stage 2 test.

Thirty-three of the 61 cases were treated either on the basis of the test results or a combination of test results and clinical judgement.

Resistance of the Heart

by Ray Peat, Ph.D.

The heart gives us some clues to our general resistance to stress, aging, disease, and death. The heart and the brain are the most stress-resistant organs, and while moderate stress and malnutrition can cause the skin and thymus gland to lose more than 90% of their substance, only the most prolonged and intense stress can cause the heart and brain to lose more than a fourth of their substance. In fact, a moderate stress that causes the thymus to shrink by more than 90% can cause the heart to increase its mass by 80%. When we are able to respond adequately and adaptively to stress, there is a transfer of substance from the lower-functioning organs (usually the skin and thymus) to the organs that are bearing the greatest burden, usually the heart and the brain.

The glucocorticoid hormones of stress play the important catabolic role of mobilizing substances from the "idle" organs to support the working organs. The many ways in which the heart is able to resist stress, and even to thrive on it can be generalized to develop ways to protect other organs, and the whole body, from the chronic and cumulative stresses that lead to generalized atrophy, declining function, and aging.

During stress, the heart and other working organs become resistant to the glucocorticoid hormones. When a person is given radioactive testosterone, it can be seen to reach the highest concentration in the heart. It is testosterone's anti-glucocorticoid effect which causes it to enlarge skeletal muscles, when exercise is moderate. Its parallel effects on skeletal muscle and heart muscle can be seen in highly adapted (stressed) long-distance runners, since the walls of their hearts become thinner as their skeletal muscles become slimmer. The other anti-catabolic steroids, pregnenolone, progesterone, and dehydroepiandrosterone (DHEA), are present in larger amounts, and are of more general importance, than testosterone, especially in the brain, where their concentration is very high. Albert Szent-Györgyi showed that the heart responds to progesterone, and more recently other researchers have presented evidence that DHEA is our "endogenous digitalis."

During moderate exercise, adrenalin causes increased blood flow to both the heart and the skeletal muscles, while decreasing the flow of blood to other organs. The increased circulation carries extra oxygen and nutrients to the working organs, while the deprivation of oxygen and glucose pushes the other organs toward a catabolic balance. This simple circulatory pattern achieves to some extent the same kind of redistribution of resources, acutely, that is achieved in more prolonged stress by the actions of the glucocorticoids and their antagonists.

Stress - a need for adaptation - can be seen as an "information gap" between the need and the possibility of meeting the need. Appropriate modification of the organism's structure closes that information gap. The new "structural trace," or memory, can develop as either a phenotypic or genotypic change. "Mutations" are important for bacterial adaptation, and learning is important for mammalian adaptation.

Stress physiology is now recognized as a universal and basic part of life, for plants and micro-organisms, as well as for vertebrates. Our brains are the newest and most powerful organs of adaptation and resistance to stress, allowing the simpler systems of circulation and metabolism to orient themselves appropriately to achieve the most benefit with the least damage. Just as there are pro- and anti-catabolic hormones and circulatory patterns, the brain has stress-promoting and stress-limiting systems. When perception and orientation govern the stress reaction, the ability to suppress certain parts of the reaction permits fine coordination and high efficiency. Sleep is a generalized stress-limiting function of the brain. Another example of how the brain governs the energy mobilizing system in stress was demonstrated by Seligman: Rats that experienced "capitulation stress," being held still until they quit struggling, drowned in a few minutes when they were put into a tank of water. But a single experience of successfully struggling to freedom caused rats to swim for many hours before becoming exhausted.

A single experience, an insight, has tremendous power to shape the way in which a rat deals with stress. Insights and ideas can be gained through practice, but they can also be passed on culturally. We can learn how to prepare ourselves to respond optimally to stress, while also trying to keep the environment from becoming too stressful.

Blue-collar workers have more heart attacks than do sedentary workers, and the "biosocial" stress of low status can be seen as a powerful factor in mortality from heart attacks. The helpless feeling of low status is analogous to capitulation stress. When stress is strong enough and long enough to overcome the multiple protective systems of the heart, the heart fails in certain well-defined ways, both functionally and structurally. But before injury occurs, the stress-limiting "self-restraint" systems of the heart, of the endocrine system, and of the brain, will have to fail. Considering some problems of blood circulation will help to see the integral nature of adaptation, when it succeeds and when it fails.

Pregnant women sometimes develop very high blood pressure. In the 1950s, when new diuretics were being promoted by the drug companies, it became standard practice to give pregnant women diuretics and a low-salt diet to control their blood pressure. It should have been obvious (and it was obvious to people like Tom Brewer who thought physiologically, rather than mechanically) that the increase in pressure was the body's response to an increased need for circulation. As the fetus grows, the blood volume must expand, to meet the increased circulatory needs of the uterus, placenta, and fetus. Two research projects showed that very large supplements of salt reliably normalized the high blood pressure in women with "toxemia" of pregnancy. Other studies showed similar results with a supplement of progesterone. When the blood volume is able to expand as needed, circulation is adequate at normal pressure. When blood pressure is forced down by administering a diuretic to further diminish an already inadequate blood volume, the circulation of oxygen and nutrients to the fetus is seriously impaired, and a huge epidemic of mental retardation and hyperactivity, associated with low birthweight, began in the 1950s, and continued until eventually the fear of malpractice suits stopped the absurd practice.

A few years ago I asked a recently graduated physician what things he would want to consider in a patient with high blood pressure. Some of his suggestions for therapy were very reasonable, but his approach made it clear that he was

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thinking of circulation in a mechanical way, exactly as a skilled plumber would go about normalizing the circulation of water, without caring very much about what the water was being used for. The circulation of blood is nicely adjusted to meet the demands of the tissues. Blood pressure increases gradually with age, and individuals whose blood pressure stops increasing with age have been found to have a shorter life-expectancy than normal. Apparently, aged tissue is less efficient, and needs a more strongly pumped stream of blood.

When I found, around 1970, that the pressure of oxygen was low in old animals and in animals that had been treated with estrogen, I tried to determine the reason for the oxygen deficiency in each case. I found that in old individuals (hamsters or humans) the blood was only about 50% oxygenated as it passed through the lungs, as if diffusion into the capillaries was impaired. Estrogen treatment (rats and humans) does the same, apparently by causing a sort of edema that thickens the lung tissue through which the oxygen has to diffuse. Both estrogen treatment and age cause other inefficiencies in oxygen transport and inefficient use in the tissues, further exacerbating the shortage of oxygen. Interestingly, recent studies show that "capitulation stress" causes the same variety of problems in oxygenation, transport, and use. In stress, even the respiratory center of the brain becomes under-active, tolerating the state of hypoxia. Since progesterone activates the respiratory center, the depressed respiration of stress is consistent with a deficiency of progesterone. (See note at end.)

When tissue oxygenation is inadequate, glucose is depleted quickly. In prolonged stress, the liver's gluconeogenic response to the glucocorticoids is depressed, as is its ability to form and store glycogen. As glucose is less available, the amount of adrenalin in the blood rises, and fat is mobilized from storage as a substitute source of energy. Free fatty acids, especially unsaturated fats, are toxic to the mitochondrial respiratory system, blocking both the ability to use oxygen and the ability to produce energy. The increased use of fats, instead of glucose, causes lipid peroxidation to increase, and promotes the release of lysosomal enzymes, the accumulation of calcium in mitochondria, the depletion of ATP and creatine phosphate, and a failure to "pump" calcium out of the cells, causing incomplete relaxation and rigidity of the heart muscle cells.

This complex of effects can be called "catecholamine toxicity." Rona, *et al.*, using isoproteronol in 1959, clearly established the existence of this toxicity. Several years ago, it was noticed that mortality in the U.S. from asthma increased greatly in the years since catecholamine therapy became common, without a corresponding increase in the incidence of asthma. It is now widely accepted that the therapy caused the increased mortality. Following Rona's work as it did, this large medical experiment can be taken as strong confirmation of the idea of catecholamine toxicity, and as a step in understanding stress sickness. Glucose depletion leads to adrenalin secretion, which causes fat mobilization, calcium-activated over-stimulation of cells, with impairment of the energy production which is necessary for recovery (by way of muscle relaxation and calcium excretion, etc.).

Broda Barnes showed that hypothyroidism causes heart disease, and also causes a tendency toward hypoglycemia. Low thyroid people compensate for the deficiency of energy and glucose (and of oxygen, for reasons similar to those mentioned above) by secreting an excess of adrenalin. Their 24-hour urine metabolites of adrenalin sometimes are 30 or 40 times normal. Recent studies that show that a moderate dose of thyroxin lowers lipid peroxidation confirm that thyroid has an anti-stress effect. The "conduction block" which occurs in hypothyroidism seems to be the same as the conduction block which develops in stress and predisposes to fibrillation. The electrical instability of the heart produced by excessive adrenergic stimulation can also make the sinus pacemaker more susceptible to vagal inhibition. (I think this effect can be observed in the skipped beats often experienced by hypothyroid people during stress or fatigue. In other situations, of long and intense stress, vagal stimulation protects against fibrillation.) In hypothyroidism, there is impaired relaxation of muscles, as seen in the Achilles reflex, or in the T wave of the electrocardiogram. This is similar to the contractural rigidity which develops in the stressed heart.

When stress is severe and prolonged, the liver loses enzymes of the detoxifying system, and also of the system that forms bile acids, causing a tendency toward abnormal lipid metabolism, including hypercholesterolemia. Thyroid deficiency limits the consumption of circulating cholesterol for steroid hormone synthesis, and both stress and hypothyroidism are associated with elevated blood cholesterol. Considering the clear and well defined toxicity of adrenalin and free fatty acids, the role of cholesterol in heart disease begins to look sort of epiphenomenal.

Fats enter and damage cells that are over-stimulated and de-energized. Calcium is a universal activator, but excess calcium is the central link in most types of cell damage. Calcium uptake and retention are promoted by adrenalin, histamine, vasopressin, energy depletion, and lipid peroxidation and by the activity of phospholipases; since calcium can activate phospholipases and lipid peroxidation, and interferes with energy production, vicious circles can develop. Excessive adrenalin and calcium also promote clotting, and - as the beta-adrenergic receptors become desensitized - spasms in the coronary arteries. Altered blood vessel tone, which can be produced by serious stress, can cause venous pooling of blood, which synergizes with the impaired relaxation of the heart to cause cardiogenic shock.

There are several systems that oppose the toxic effects of adrenalin. GABA, dopamine, and adenosine have multiple anti-adrenergic effects. In many situations, the parasympathetic system is protective against adrenalin. The protective steroids also act at many levels. Magnesium, retained in the cell largely under the influence of ATP and thyroid, is our basic "calcium blocker," or calcium antagonist. GABA and dopamine inhibit the ACTH-glucocorticoid system, and shift the steroid balance toward the protective anti-glucocorticoids, progesterone, testosterone, pregnenolone, and DHEA.

Adequate glucose and oxygen are the most important anti-stress substances. "Overload" of an organ means that the blood isn't delivering enough oxygen and glucose to sustain the needed level of functioning. Thyroid and progesterone

tend to prevent overload by increasing respiratory efficiency, and by increasing the liver's glycogen storage.

Uridine, a co-factor in glycogen synthesis, can also prevent stress by improving glycogen storage.

Anti-oxidants, especially vitamin E, prevent tissue damage by promoting normal oxidation.

Selye's demonstration of corn oil's toxicity to the heart is an important link in the general picture of stress injury and adrenalin toxicity. The protective effects of saturated fats are not surprising when seen against the background of the toxic effects of adrenalin, causing the mobilization of fatty acids and the resulting lipid peroxidation.

Meerson's demonstration that gentle adaptation to hypoxia (similar to treatment with thyroid hormone) can prevent heart damage from subsequent intense and prolonged stress, is similar to Seligman's discovery that rats can be protected against stress by an experience of escape, but Meerson has surveyed a great range of protective processes, ranging from the subcellular level to the most highly evolved brain systems. In thinking about Meerson's achievements in protecting the heart against stress, it is important to remember that the heart is our most stress-resistant organ, and that the things that protect the heart from deadly stress will also protect the other organs from the everyday stresses, which accumulate to cause the problems of general aging. Liver, lungs, pancreas and other essential organs are susceptible to the same kinds of damage as the heart, but under conditions that are relatively mild and ordinary.

The resistance of the heart and liver can be compared in several ways. For example, DNA replication is more easily suppressed by stress in the liver, than in the heart, but DNA repair is not affected in the same way by stress. Hyperfunction of the heart stabilizes DNA against injury, so DNA repair is greater in the liver than in the heart, and is least in the brain.

Meerson's laboratory has studied the anti-stress and anti-adrenalin effects of GABA and its metabolite, gamma-hydroxy butyrate, especially in the form of the lithium salt. (Lithium seems to have its own anti-stress effect, probably partly as a sodium agonist, and partly through its ability to complex with the ammonium which is produced in the brain in fatigue, which is exactly when the GABA system becomes active.) GHB is protective against stress damage to many tissues. It prevents stress-induced enzyme leakage from tissues, ulceration of the gastric mucosa, lipid peroxidation, epileptic seizure, damaged contractile function of the heart, and cardiac arrhythmias produced by stress or ischemia.

Meerson's group has also studied the protective effects of the gamma-butyrobetaine derivatives of the sort that are normally produced in the brain and heart, or that have been synthesized or extracted from plants. These substances stabilize the heart rhythm in acute

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Resistance of the Heart

myocardial infarction, and also in postinfarction cardiosclerosis (page 173, *Adaptive Protection of the Heart*, F.Z. Meerson, CRC Press, Boca Raton, 1991). They have a protective action against both adrenalin and calcium. Interestingly, atropine potentiates the protective effect of the butyrobetaine against calcium toxicity.

A complete list of protective nutritional chemicals and natural drugs or analogs to our endogenous protective factors would be very long, but we should give special thought to certain ones, including succinic acid, which stimulates respiration and protective steroid synthesis; thyroid and vitamin E, which promote normal oxidation while preventing abnormal oxidation; magnesium; sodium and lithium, which help us to retain magnesium; tropical fruits, which contain GHB; coconut oil, which protects against cardiac necrosis, lipid peroxidation, hypothyroidism, hypoglycemia, and histamine damage; valium agonists, natural anti-histamines; adenosine and uridine. Visits to higher elevations, and exposure to bright, long-wave light, can cause the body to optimize its own anti-stress chemistry. Avoiding the sense of being trapped is a high-level adaptive factor.

Note: The consistency with which oxygen becomes deficient in aging, stress, and estrogen excess suggests that a basic coordination mechanism may be involved, in which there is a shift toward the conditions which will activate the expression of certain genes - possibly the hypoglycemia-stress-heat-shock proteins, or possibly simply the proteins of cell division and growth.

The life-span of cell organelles, DNA, and essential enzymes, is extended by adaptation. The cellular (membrane phospholipid) composition adjusts toward a lower content of unsaturated fatty acids. (S. Gudbjarnasson, et al., "Modification of cardiac phospholipids and catecholamines in stress tolerance," in *Alpha-tocopherol, Oxygen, and Biomembranes*, C. DeDuve and O. Hayashi, Eds., Elsevier/North Holland Biomed. Pr., Amsterdam, 1978, p. 297.) Diacylglycerol causes activation of transcription, cell growth, and proliferation. (G.L. Hammond, et al., "Diverse forms of stress lead to a new pattern of gene expression through a common and essential metabolic pathway," P.N.A.S. 79, 3485, 1982.) Stabilization of mRNA splicing and protein synthesis (H.G. Yost and S. Lindquist, "RNA splicing is interrupted by heat shock and is protected by heat shock protein synthesis," Cell 45, 185, 1986) suggests the possibility that this system might also be important in viral immunity.

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P.S.: Pavlov's turn-of-the-century work on the heart's "trophic nerves" should be re-examined in the light of this new information on the trophic effects of adaptation.

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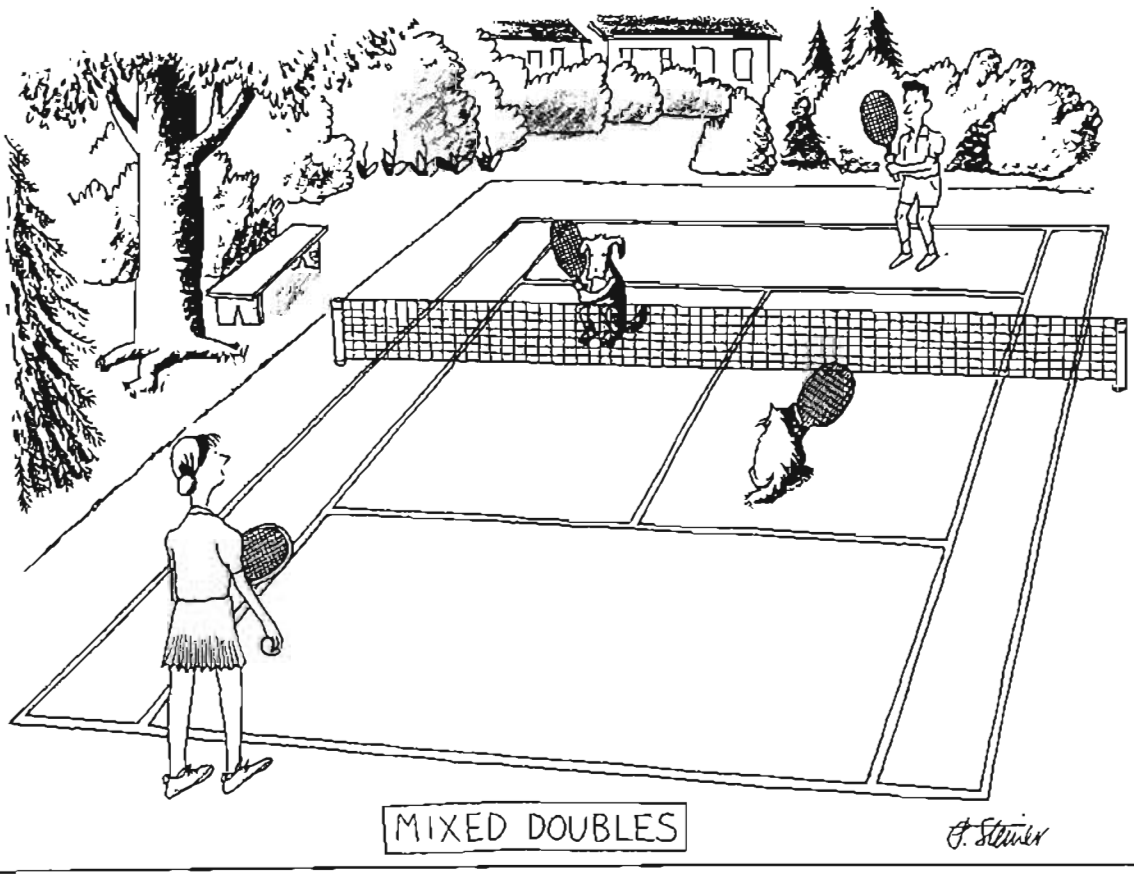

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Ray Peat's Repairing

Last summer's death of most of Europe's seals from viral diseases suggests the possibility that their immune systems were weakened. The coincidental publication last spring of a study of the relatively remote Arctic seals of Spitzbergen,[1] which found surprisingly high levels of dioxins and other toxins in the animals, suggests that the aquatic carnivores closer to the sources of pollution might simply have been the first large group of animals to reach an intolerable level of chemical immunosuppression. The people who eat the same fish that the seals eat, and breathe the same air, might also be experiencing some degree of increased susceptibility to infections.

For several decades, the death rate from some kinds of opportunistic infection has been increasing,[2] and as bacterial infections came under control in the 1960's they tended to be replaced by less common infections such as *Pneumocystis carinii*.[3] Acquired (or secondary) immune deficiency has been a familiar phrase in immunology for at least a generation, and the recognition of the condition itself, under different terms, has been part of medical knowledge for many generations. Before 1981, typical textbooks listed cancer, chemotherapy, ionizing radiation, malnutrition, aging, parasites, fungal infections, and viral infections among the known causes of acquired immune deficiency.[4]

After 1981, the term "acquired immune deficiency syndrome" was appropriated by the molecular virologists, who were familiar with the ability of viruses to cause immunosuppression, and who, with impressive speed, determined that the "new" syndrome was caused by a certain new virus, the human immunodeficiency virus (HIV) or the human T-cell lymphotropic virus type III (HTLV-III). Peter Duesberg was one of the few molecular virologists who doubted that a virus of that sort, all by itself, could cause disease.[5] An important implication of the identification of the HIV as the cause of AIDS has been – for the molecular virologists who ignore Duesberg – that a specific vaccine or genotoxic chemical should be able to destroy the specific pathogen. Very little attention has been given to the question of whether a person's good health can be maintained despite the presence of the "viral gene." And the lingering effects of the "central dogma" of molecular genetics still discourage serious investigation of the question of whether such genes can be cleared from the genome under certain conditions without destruction of the cell.

Since human exposure to known immunosuppressants has been increasing during the years that the incidence of opportunistic infections has been growing, a real investigation of the cause or causes of AIDS will involve doing some scientific epidemiology, to learn whether some factor other than the HIV has a crucial role. Some of the factors that I have given attention to, in working with "ordinary" (i.e., complex, traditional) immunodeficiency – viz., a deficiency of the anti-glucocorticoid hormones, a dietary excess of iron and unsaturated fats,[6] a nutritional deficiency of vitamin A, folic acid, copper, and protein, an exposure to pediculocides and other chlorinated hydrocarbons including dioxins, etc. – should probably be included in such an epidemiological study. Even if such factors turn out not to be crucial in AIDS-HIV, my informal studies and observations since 1973 indicate that examining and correcting as many of them as possible can, inexpensively and safely, promote recovery from many chronic infections and other diseases associated with some degree of acquired immunodeficiency. Whatever the cause of AIDS associated with viral infection may be, it is likely that an appropriately designed supportive treatment will at least slow the progress of the disease.

In spite of a few virologists who still claim that there is no such thing as an immune stimulant, hundreds of immune-promoting substances have been studied and described, and a few of them (e.g., levamisole, inosiplex) are well-known. Although more meaningful tests are now available, skin tests have been used for several decades to demonstrate that immune stimulants or improved nutrition[7] can reliably shift the immune system from anergy to reactivity. Anything that intensifies metabolism tends to be an immune stimulant, other things being equal. A subnormal temperature is a common feature of chronic infection and early cancer, until a late stage of intense

catabolism with fever. Since most of the immune stimulants are harmless, compared to the genotoxins, the reluctance to test them is ideological, rather than scientific. My Stedman's Medical Dictionary (23rd edition) illustrates the psycho-linguistic environment: "immunodeficiency" and "immunodepressant" and "immunosuppressant" are defined in a way that any native English speaker would understand. However, "immunological enhancement" (p. 464) is explained as involving the *suppression* of cell-mediated immunity (to prevent rejection of a tissue allograft). A major part of the history of medicine seems to have dropped out of medical English.

In one line of thinking a variety of malfunctions of immunity can be created by a single factor, such as energy deficiency, acting within the organism's special history or constitutional individuality. Allergies, auto-immune disorders, and chronic infections or skin-test anergy, can be seen as aspects or phases of a generally impaired reactivity of the organism, shaped by many trophic influences of nerves, hormones, nutrition, and by toxins, temperature, radiation, etc.[8] Accordingly, I have recommended the use of techniques of immunity-promotion (or normalization) for allergies, auto-immune disorders, and chronic infections or immune deficiencies, taking into account the person's history of environmental insults, nutritional deficiency, family traits, and present hormonal, nervous, and metabolic status as far as possible.

Beginning in 1973, a clinic in Eugene, Oregon (a city which is notorious for allergies, because of the surrounding grass-seed farms which produce pollen in the spring, and smoke from field-burning in the summer and fall) had very good results with their allergy patients when they gave them supplements of vitamin A, pantothenic acid, and vitamin C. Later, thyroid extract or triiodothyronine and magnesium were added to the other supplements for patients who had problems more serious than ordinary allergies. We found that many people with acne, bladder or kidney infections, periodontitis and sinusitis seemed to be deficient in both thyroid and vitamin A even when they were taking supplements of those materials. At higher doses of both, many of those people quickly got over their infections. Many people with colitis, myositis, bursitis and arthritis had sudden relief from their symptoms on this, or a similar program. We have assumed that some toxin might be interfering with the biological effects of thyroid and vitamin A.

If thyroid and vitamin A can't be used efficiently to form steroids, a steroid imbalance is likely. Unopposed cortisol is immunosuppressive in several ways, including thymic hypoplasia,[9,10] depression of the histaminolytic activity and mono-oxygenase activity of the liver, contributing to chronic allergies,[11] and it can induce the expression of some types of retrovirus.[12] Although one of the important functions of vitamin A is its involvement in the formation of the steroids pregnenolone and progesterone (both of which moderate the effects of cortisol), it also has some hormone-like actions directly on the cells of the immune system, and it stimulates production of interleukin-2 and both inhibits generation of specific suppressor cells and limits the intensity of activation of suppressor cells.[13] The possibility of vitamin A toxicity is reduced by using the thyroid hormones and vitamin E. Pregnenolone and progesterone have a vitamin A-sparing effect, besides their direct protective action for the thymus, and they also have the very general protective action which Selye called "catatoxic." Both of these hormones have been effectively used to treat various auto-immune ailments. They tend to raise the body temperature and metabolic rate, yet they are anti-catabolic.

Vitamin A, thyroid, progesterone, and the related steroid, dehydroepiandrosterone, all oppose estrogen, which has several immunosuppressive effects, including a cortisol-like thymic atrophy, hypoactivity of T cells, and reduced production of gamma-interferon and interleukin-2, reduced natural killer cell activity, and it probably has a role in the development of some auto-immune diseases.[14] Subnormal body temperature promotes estrogen secretion.

AIDS, which has been called "slim disease" in Africa, often ends with extreme wasting. Many physicians are horrified at ➤

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the thought of treating immunodeficiency with thyroid, because they associate hyperthyroidism with weight loss. Two young women, who were diagnosed as having "allergies" and supposedly autoimmune pituitary hormone deficiency, and who each weighed around 70 pounds and was considered to be "terminal" (though they both ate normal amounts of food), recovered quickly with a thyroid supplement and a diet emphasizing eggs and fruit. About 80 years ago, when surgery was first being done to remove goiters, the whole gland was removed, no supplementary thyroid hormone was given, and the patients often died of a wasting syndrome, which was named "cachexia strumipriva." Thyroid function is essential to all cell processes, including protein assimilation and synthesis, formation of growth hormone, etc. Without thyroid hormone to sustain respiration, inefficient glycolysis wastes energy; unoxidized lactate provokes catabolism of liver protein. Hypoglycemia stimulates secretion of glucocorticoids, which maintain blood sugar at the expense of rapid catabolism of protein. It is characteristic of people dying with AIDS to have no thymic tissue, as well as having other signs of extreme stress. It seems clear that a safe anti-stress, anti-cachexia, thymus-protecting program would have prolonged their life. Triiodothyronine is often the essential factor in reversing a cachectic state. Although optimal thyroid function can increase the metabolic rate, it is not catabolic because it maximizes bioenergetic efficiency.

Adamkiewicz demonstrated the importance of blood glucose in anaphylaxis and allergy.[15] In a vicious circle, histamine tends to exacerbate hypoglycemia (e.g., by its acetylcholine-like actions) and it is directly immunosuppressive in many ways. It inhibits lymphocyte proliferation in response to stimulation, it inhibits antibody formation and lymphocytotoxicity, it suppresses cutaneous delayed hypersensitivity and release of lymphokines, and it suppresses both the generation of T-helper cells and their effector functions.[16-19] Besides the ordinary antihistamines and receptor blockers, the release of histamine can be inhibited by many other substances which are immunoprotective, such as epsilon-aminocaproic acid, and by the saturated fatty acids, from pentanoic to dodecanoic.[20] These fatty acids are known to be assimilated as quickly as glucose, and so it seems likely that part of their antihistamine effect is similar to the glucose effect demonstrated by Adamkiewicz, and that both effects could be largely the result of increased availability of metabolic energy. Since tumors often contain very large quantities of mast cells, immune therapy for tumors should take histamine into account. Since 1970 I have experimented with some unconventional anti-inflammatory substances, including some of the local anesthetics, which seem to have a safe and effective antihistamine action. I think some of the anti-cholinergics which have "anti-viral" activity (e.g., amantadine) are analogous in their mechanisms of activity.

Around 1960, ammonia was found to have an "anti-viral" effect, apparently by altering the host cell's structure or function, rather than by a direct virucidal action.[21] Following that discovery, many amines were found to have some anti-viral activity. Local anesthetics, anti-cholinergics, and the anti-viral amines can be thought of as a pharmacological family. Inosiplex apparently takes advantage of some of those properties, and it too acts on the cell, rather than on the virus.[27]

We found that many people with acne, bladder or kidney infections, periodontitis and sinusitis seemed to be deficient in both thyroid and vitamin A even when they were taking supplements of those materials.

The central inhibitory system regulated by gamma-aminobutyric acid, the GABA-ergic system, is protective against stress,[22-24] and appears to protect immunity by limiting the organism's recourse to cortisol, and by supporting the synthesis of alternative steroids.[25,26] Gamma-hydroxybutyrate and its lactone are closely related to GABA metabolic pathways, and have anesthetic and anti-stress protective effects which appear to result mainly from central inhibition, and from an anti-glucocorticoid effect. The lactone has been found to have a strongly protective effect against intra-cerebrally inoculated viruses,[28] and it is remarkably non-toxic. The anesthetic and anti-convulsant effects of progesterone probably synergize with and reinforce the GABA-ergic system.

Many other substances of low toxicity have beneficial effects on the immune system or on some other aspect of resistance, and might be considered in an integrated approach to immune restoration.

Just as optimal nutrition must take age and other factors into account, an integrated therapy for immune deficiency must be sensitively designed for the needs of the individual. In many places where AIDS-HIV patients are treated, a panic mentality has taken over, and ordinary supportive therapies are neglected or rejected because they are outside of someone's "treatment protocol." A stereotyped protocol can be appropriate when therapy is directed toward the mechanistically understood elimination of a pathogen, but in therapy to strengthen immunity, individualization, alertness, and judgment are more appropriate. The complex nature of every patient should be recognized, in deciding what materials to use and how to use them.

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Repairing Immunodeficiencies

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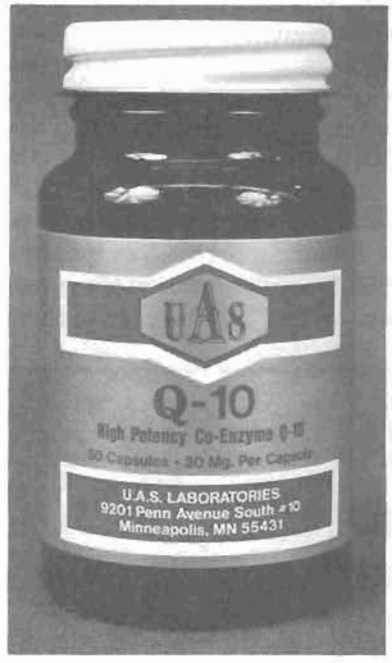

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Letters to the Editor

Dubious Uses of Paper, Postage and Reader's Time

Editor:

Your planned price increase "due to recent increases in paper cost and postage" raises a sore point with me. As a subscriber since 1985, I have a friendly suggestion.

I wish *TLfDP* would *decrease* use of paper and postage by being more selective about what it publishes. Too much of *TLfDP* is rambling, half-baked, unreferenced or otherwise of low use. This problem is getting worse – or my patience for it is going down (or both) – as the size of the magazine has expanded over the years. *TLfDP* becomes less welcome to me as it takes longer to search through the chaff. To pay more for less is doubly unwelcome. I understand your ideas about peer review (July 1993, p. 740), but for me they are now colliding with too many pages.

What I like best about *TLfDP* includes literature abstracts with brief commentary, news of many kinds, brief hypotheses, and the more factual, thoughtful book reviews. What I like least are windy essays, overly long letters and inadequate references.

Here are two examples of dubious uses of paper, postage and readers' time:
1. "Enzyme Therapy. An Effective Alternative for Musculoskeletal Problems," by Anthony Cichoke, Nov. 1994, p. 1183-85. The first 90% discusses the dangers of corticosteroids, with 26 references, *but with no mention of the title subject.* The last 10% dealing with enzyme therapy cites *not one reference.* Yet the author concludes with a straight face that "Enzymes are a proven and effective" alternative to steroids.
2. Article on coconut oil, by Ray Peat, June 1995. Page 156 (last paragraph) says, without references, "The anti-obesity effect of coconut oil is clear in all the animal studies." Intrigued, I looked for such studies in Medline. I found none. So I wrote to Peat 7 weeks ago asking for key references, including for his additional claim of cholesterol lowering. I've received no reply to date.

Communication and information are valuable. Bluster and unreferenced "facts" are not. I wish *TLfDP* would increase the ratio of the first to the second, or print *fewer* pages, not more. I don't have unlimited time for an unlimited, unselective *TLfDP,* and I doubt that many practitioners do either. I suggest you poll readers about the growing size of *TLfDP* and what parts they value most. For me *TLfDP* has become too large to be so unselective.

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Ray Peat, PhD Replies

Thanks for passing on the comments from D.R. Davis, PhD I haven't received his letter asking me for references, and I assume it's because my Mexican address was listed with the coconut oil article. (I'm back in Eugene, Oregon).

Davis mentions that he looked in Medline for references to the animal studies I wrote about. Practicing physicians, who put in long hours with their patients, and who work in the context of an often authoritarian profession and an oppressive bureaucratic culture, need to find out in an efficient way what other physicians are doing, and they probably find Medline and Index Medicus very useful. But for a research scientist working in a college of natural sciences, in a university with a good library, there are more appropriate ways to search – especially since I emphasized that some of the work was done more than 50 years ago.

I decided to take a random sampling of Medline's information. (I noticed that the library's machine advised that Medline not be used if you are looking for information on non-human animals). I looked at their entries for 1984, where I found F. Berschauer, et al., "Nutritional-physiological effects of dietary fats in rations for growing pigs. 4. Effects of sunflower oil and coconut oil on protein and fat retention, fatty acid pattern of back fat and blood parameters in piglets." *Arch. Tierernahr* (East Germany) 34(1), 19-33, 1984. [Fat content in the coconut oil fed animals, after only 34 days, was 15.9%; in the control group, 18.6%; and in the sunflower oil fed animals, 21.1%.]

So, I saw that Medline does include an animal-nutrition journal, and decided to check another year. J. Yazbech, et al., "Effects of essential fatty acid deficiency on brown adipose tissue actvity in rats maintaind at thermal neutrality." *Comp. Bioch. Physiol. A* (England) 94(2), 273-276, 1989, suggested that the observed increase in resting metabolic rate produced by using coconut oil to create an essential fatty acid deficiency, is partly the result of increased heat production in the brown adipose tissue. The weight of that fat decreased by 28%, while its ability to produce heat increased 69%.

If Davis checked a data-base that was designed for animal research, he could find an abundance of publications relevant to the queston of coconut oil's effect on body fat. I don't know of any computerized data systems for biology that go back 60 years, but manual searching of the printed sources is only a little slower than the electronic method, and infinitely more precise. Over the years, I have noticed that science libraries seem to be off limits to most professors, so any information they can get from computers should be significant, but the reliance on computer-retrieved information puts an awful burden on the people who choose the keywords.

The *Townsend Letter,* especially with your new title, is obviously a journal of viewpoint, and not of technical data. As such, much of its function is to clarify goals, orientations, and beliefs, and possibly to encourage people to have more imaginative, flexible, and critical attitudes toward medical ideas. When a publication purports to be objective and "scientific," then there is a problem with unsupported assertions. If Davis

had complained, for example, that an article in the July/August *Scientific American Science and Medicine* by D.V. Spicer and M.C. Pike was doctrinaire, ideological, and promotional, and failed to support most of its important assertions, I would think his letter was constructive. But I think he misunderstands the *Townsend Letter's* reason for existence. Although it isn't at all the sort of "alternative health" journal I have imagined publishing, its openness is important in this increasingly repressive medical-bureaucratic environment.

The refereed journals are not great critics of themselves. Some appalling things happen at the "great journals," but the scientific-medical reader generally assumes that the editors fairly select representative experts to review the submitted work. Venality, bigotry and plagiarism are probably just as well represented in the main-line professional journals as in other parts of our society. The greatest abuses are possible when the referees are anonymous. A series of shocking experiences with journal referees over a period of 15 years led me to stop submitting my work to professional journals in the U.S. There are only a few small journals that I think are respectably free from the corrupting influence of corporate power.

In 1981, I began a newsletter to keep my friends informed of my progress. Occasionally, these almost private communications get wider distribution, as when the *Townsend Letter* picks them up. I am glad to offer a few readers some background sources and occasionally some additional material I didn't cite in the newsletter, but when someone is making their first approach to an area of research, I think the best method is to ask a science librarian to help them.

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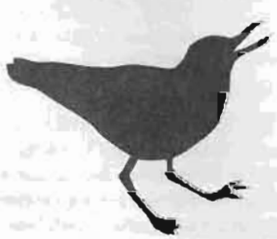

Enzyme Therapy: An Effective Alternative For Musculoskeletal Problems

Editor:

In response to Donald R. Davis, Ph.D.'s letter I would like to offer the following comments.

A review of my article ("Enzyme Therapy: An Effective Alternative for Musculoskeletal Problems") indicates that his statement regarding a lack of references in the enzyme therapy section of that article is correct. Somehow, the references which substantiated enzyme therapy did not appear in that article. I honestly don't know how this happened. But I am the author, and the buck stops here.

The *Townsend Letter for Doctors* is a vital, essential avenue for presentation of information on alternative therapies. Therefore, when a concept is presented, the readers have the right to know the source of this information and to be presented with substantiating references. This is an extremely valuable periodical, one which has the strength to present new information and controversial topics. Therefore, each author has an extreme responsibility – a trust to document all statements he or she makes and to be able to defend his or her position, based on the articles referenced in the manuscript.

Although subsequent enzyme articles have substantiated many of the points made in the November, 1994 article, each article must stand on its own.

Therefore, I apologize to the *Townsend Letter for Doctors*; to its fine readers; to my research mentors at the University of Minnesota, University of Rochester, Eastman Dental Center, and Case Western Reserve University; the Ph.D.s and M.D.s (in universities and research institutions) throughout the world who did not have the opportunity to substantiate their concepts on systemic enzyme therapy through the referenced bibliography, and finally to Dr. Davis.

The hundreds of research articles on systemic enzyme therapy verify its effectiveness for a multitude of conditions. Each reader has the right to know why and where to go for further verification.

For additional substantiation, please see previous and future *Townsend* articles on enzyme therapy, my book: *Enzymes and Enzymes Therapy: How to Jump Start Your Way to Lifelong Good Health*, and the article in this issue of the *Townsend Letter for Doctors*.

The following is a referenced rewrite of the section, Enzyme Therapy: An Alternative Course of Action, that appeared on page 1185, *Townsend Letter for Doctors*, November, 1994:

Enzyme Therapy: An Alternative Course of Action

In recent years, researchers have offered alternatives to the use of cortisone therapy for musculoskeletal problems.[27-50] Systemic enzyme therapy appears to be a viable alternative with none of the serious side effects so often noted with cortisone.[49]

Conservative health care and systemic enzyme therapy can help contain costs and provide a greater sense of patient satisfaction.

Enzymes are effective in treating various conditions (both acute and chronic)[51,52] because they:

- Inhibit edema[53,53]
- Activate fibrin degradation[54-57]
- Interact with prostaglandin synthesis[58,59]
- Degrade complement-activating immune complexes[60-71]
- Stimulate the function of antibodies[71-74]
- Improve plasma viscosity[51,71,73,75-78]
- Reduce atherogenetic lipids[73,79]

Conclusion

Although adjustments and soft tissue techniques are the prime chiropractic tools, their success can be greatly influenced by musculoskeletal and total body health.[80] Cortisone therapy can interfere with the body's innate capacity to maintain health and to fight disease.

Enzyme therapy seems a viable and natural alternative to caring for musculoskeletal problems when compared to the serious and long-term side effects of cortisone. Enzymes are a proven and effective tool that should be implemented by practicing alternative

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More Letters

Progesterone Content Corrected

Editor:

Burton Goldberg's article on fibroids (January, 2000) on page 90 indicates that Aeron LifeCycles lab reported the progesterone content of Progest-E Complex as being between 1,000 and 1,500 mg. per ounce. I was told a couple of years ago that this figure was mistakenly introduced into John Lee's book by the book's editors. That product, made under my patent, has never deviated from its 10% progesterone content, so it contains 2,850 mg of progesterone per ounce, and I don't know of any test that has found otherwise. As I understand it, Dr. Lee's book was later corrected.

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Evidence Links Viruses and Bacteria to Gallstones

Editor:

I read with interest your excellent publication and would like to comment on the article "Mounting Evidence Links Viruses and Bacteria to Everything from Cancer to Gallstones" in October 1999 issue (page 39). I forward an article from my health information course which your readers may find interesting. Any references to it being a course article could be omitted as it makes a free standing item also.

The toxic state of tissue is of primary importance whether in cancer or gall stones (two items mentioned in article heading). Without dehydration, gall stones cannot form and I believe that the common factors in all chronic ill health are dehydration, toxicity and chemical (nutritional) imbalance. Bacterial clean-up is a result, not a cause, of such a dry, toxic and nutrient-imbalanced state. Of course, individual constitution and toxic/nutritional history make necessary the evaluation of each person on an individual basis.

I find the author's comments most interesting and if these are seen in the light of being the result and not cause of illness, this work would complement works of people like Béchamp, Lida Mattman and many others who also identify microbes at the site of "tissue activity."

The herbs he mentioned are most interesting and beneficial in that they aid tissue detoxification and immune capacity and therefore enhance and shorten the tasks of 'pathogenic' microbes. I agree also, that the quality of herb is of vital importance.

The philosophies of Pasteur versus Béchamp are a most important fundamental foundation in thinking upon which to place the evidence of what we find. In short, Pasteur believed that microbes are from external sources, unrelated to tissue state and need a solution from without (i.e. drugs – the basis of the pharmaceutical industry). Béchamp believed and *proved* that microbes originated from within, when the climate was toxic, and reverted to non-pathogenic microbes when tissue returned to health. This philosophy is the basis for health and responsibility. Pasteur renounced his beliefs and agreed with Béchamp on his death bed, but that is not commonly known nor reported. Béchamp for some strange reason, despite his impressive titles and works, has been larely ignored and deleted from records where he should have been found.

Some may ask how the Australian Barry (?sorry cannot recall his surname) 'infected' himself with *H. pylori* when he was identifying its asociation with stomach ulcers. In my experience the stomach lining is badly affected by chronic dehydration and mercury poisoning from fillings. I wonder what this experiment would have produced in a non-toxic (realistically in the 1990's low-toxic), well hydrated individual. Sorry Barry – not being personal – only discussing the parameters of possibilities. How do children pick up 'infection' from peers if there is no contagion? Well, there is an opportunity to 'catch detoxification agents' if relevant to your tissue. Resonance is the key. Why do only certain office staff 'catch' the cold going around? Why not everyone? Resistance is the usual understanding but examining resistance brings one back to the terrain theory of Béchamp. Also, how can some have 'TB' of the lung in the absence of the *tuberculus bacillus?* If we are going to keep to the laws of good science then 'contagion laws' apply to all.

Alas, health for all would topple society as we know it. The food industries, banking and finance systems, petro-chemical industry, pharmaceutical industry and indeed, government revenue etc. all rely on the premise of Pasteur.

The sickness industry, massive and international, is nothing to do with health. I am certainly not against society etc. and the sickness industry offers the only help some will accept – I am not pointing fingers or involved in criticism, but simply state that the choice for health is individual and cannot be truly made unless based on the necessary information (Informed Choice). There are many who do not choose health and that is their prerogative. Information is plentiful but putting it together in context to get a clear picture is not easy. Your publication serves as an excellent forum in this respect.

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Detoxification and Its Erroneous Label of 'Infection'

V. Bradshaw 1996©

In my experience of helping people to resolve their health problems, I have encountered various attitudes to getting well.

- Some desperately want rid of their symptoms but only if they do not have to be involved – they seek the magic bullet from without. I am usually unable to help a person with this approach.
- Others are prepared to do some things which do not inconvenience them too much. These people may receive some help.
- There are others who really do want to get well, are prepared to take back the responsibility for their own health and see their symptoms as no longer necessary as they implement changes – some of them quite drastic ones. These people embark upon a

More Letters

Progesterone Can Be Taken Orally

Editor:

Your June review of Betty Kamen's book on hormone replacement in menopause, osteoporosis, and PMS made some good points, but it repeats a serious error, that progesterone "cannot be taken orally."

I believe that idea was a simple fabrication of someone in the drug industry in the 1940s to promote their own new synthetic progestin, because I could never find the source for the idea, which simply began appearing in the literature without supporting data, when new products needed promotion.

Human milk from healthy women contains significant amounts of progesterone, which makes milk an important part of the infant's endocrine system. Associated with fat droplets, progesterone enters the blood by the chylomicron pathway, permitting it to avoid inactivation or excretion.

When taken in the powdered or micropulverized form (even if the powder is packed in oil) progesterone doesn't enter the blood as chylomicrons, and so is quickly processed into a water-soluble metabolite, which is excreted. This metabolite cross-reacts with active progesterone in the usual analysis of blood levels, and creates some medical confusion, since symptoms and measurements don't relate in the usual ways.

Betty Kamen cites my book, *Nutrition for Women*, as a source for the idea about oral progesterone. I believe she might not have read my material itself, since my comparisons in that book had to do with the superiority of skin-absorption over injected progesterone. In many other publications, including *Progesterone in Orthomolecular Medicine* (all my books are available directly from me), and several articles in the *Townsend Letter*, I have described the efficacy of oral progesterone dissolved in vitamin E.

I have the patent on that form, and some manufacturers have unscrupulously implied that they are using my formula. I have tested several such preparations, in preparing my patent infringement case. Recently I have examined some of the products of a Portland company (a company which has led many people to think I am involved in their business). What I found was that the progesterone had rapidly gone out of solution, forming bizarre hair-like crystals, which gave the solution a slightly stringy texture. Natural progesterone in natural vitamin E remains stable in solution, and I believe the only explanation for the bizarre crystallization that I and others have observed would be the use of synthetic polymer-substances in the solution. In that form, it doesn't infringe my patent, but it would seem to be mislabeled and misrepresented.

The FDA has erroneously classified progesterone with synthetic progestins, and hasn't made any attempt to help the public separate promotional fictions from physiological facts. In fact, they have themselves created additional fictions about progesterone, ascribing properties of the synthetic progestins to progesterone itself, resulting in tremendous injury to the public health. (If that agency strictly followed the rules of administrative law, it might not be perceived as the servant of the industry which it is supposed to regulate.) The ineffectiveness of oral progesterone is one of the fictions that needs to be corrected, and the popular and alternative medical press is where that correction can be achieved. Betty Kamen's book is better than most of the books on osteoporosis and menopause, but it looks a little too much like a promotional effort in support of Dr. Lee's cream, and I am sorry that one of my books is mentioned as seeming to support the fiction that the skin cream is better than the oral oil form.

If she ever rewrites the book, I hope she will consider the evidence that thyroid hormone plays a major role in rebuilding bones, and that unsaturated oils (via prostaglandins and a variety of other hormonal derangements) and estrogen (via promotion of prolactin) have a role in *causing* osteoporosis. Oral progesterone dissolved in vitamin E is a powerful protectant of every system and tissue, including the bones, but it is important to understand its wonderful effects in the contexts of physiology and ecology. I think the properties of natural progesterone provides us with a scientific paradigm, similar to the concept of "adaptogens" in medicine, but even more basic, involving physical self-ordering processes. Increasingly, our health will depend on understanding this paradigm of life's resistance to harm.

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Rosacea, Rhynophyma, Pterygium & Riboflavin — & Varicose Veins

by Ray Peat

Several times lately I have heard that the cause of rosacea is unknown; for example, in Dr. Donohue's newspaper column, he wrote that "we don't know the precise cause," but then said that "hot beverages and spicy foods can contribute to such enlargement; so does alcohol." For many years I have assumed that the cause was known to anyone who cared to know, so I think it might be useful to describe some case histories, and some processes that relate to the cause.

In 1964 a somewhat alcoholic neighbor of mine was interested in improving his memory, since he had trouble finding the words he wanted when speaking or writing. His nose was remarkably red, but at the age of 41 or 42 it was not noticeably enlarged. I suggested many times that riboflavin might help, since I inferred from his very vascularized nose that his tissues were experiencing relative hypoxia, and that his brain tissue might be suffering even more than his nose, since such extensive new growth of blood vessels would seem less likely throughout the brain. For several weeks, he kept coming back asking me to remind him what it was that I had suggested; I started giving him notes, but he mislaid them. Finally he retained one of the notes long enough to ask his doctor to give him some vitamins, and the doctor prescribed daily injections of the vitamin B complex. I saw him in the afternoon a few hours after his first injection, and was surprised to see that his nose was no longer red; he spoke fluently and quickly, and did not have to search for words. Each day that week he returned for more injections, and both his nose and his memory stayed healthy. However, over the weekend, when the doctor's office was closed, both problems returned in full: his nose was as red (and shiny) as ever, and he struggled for some word in almost every sentence. By Monday it seemed that he had forgotten the whole episode, and didn't return for more injections.

I moved away around that time, and didn't see him again until 1976. At that time, his nose didn't seem particularly red, but it had enlarged and become very lumpy—a potato nose, or rhynophyma. (Rhynophyma is considered to be an advanced, hyperplastic form of rosacea.) He had undergone surgery for defective heart valves, but seemed to be in good health except for occasional nosebleeds. (He died in 1985.)

Before learning that he had nosebleeds, it had occurred to me that bloodshot eyes and a red nose probably have internal equivalents, which might be revealed as nosebleeds in some individuals, and as strokes in others. I knew a woman whose four year-old son had very frequent nose-bleeds that usually occurred around one or two AM during sleep, or during daytime naps. He also had frequent violent rages, that seemed to happen after he had eaten certain foods, usually cookies or cake. I reasoned that a riboflavin deficiency would waste glucose by blocking mitochondrial respiration, and that blood vessels would dilate to deliver more blood to the tissues. Since blood sugar falls at night, I thought this could account for the regularity of his night-time nosebleeds. His frequent angry behavior seemed to be an exaggeration of the normal irritability of hungry children. His mother had some distinct mental problems, which had included a classical postpartum psychosis. She wore contact lenses, and I noticed that she had chronically visible blood vessels in her eyes, mainly on the side toward her nose. The area was yellowed, and lumpy. Close inspection suggested that the vessels had become increasingly enlarged, numerous, and tortuous, until the surface of the eye was distorted by the excess of blood vessels.

The cornea normally has a high concentration of riboflavin, but it is very susceptible to a deficiency of that vitamin. It receives its oxygen largely directly from the air, and partly from the ring of blood vessels at its edge, which are supplied by vessels approaching from the two sides. In her case, it seemed that the contact lenses, shutting off direct contact with the air, had led to an invasive growth of blood vessels to the edge of the cornea, probably partly because of a riboflavin deficiency.

I think this would be called a pterygium, but I think the same kind of process would be called rosacea if it occurred on the nose or cheeks. Oxygen deficiency causes connective tissue cells to produce extra collagen. This would intensify the problem of delivering oxygen to the cells, tending to set up a vicious circle. Even normal levels of riboflavin and other nutrients and oxygen in the blood wouldn't be enough to allow the necessary amount to reach the cells, once the lumpy fibrous overgrowth had begun to develop.

I gave the woman and her son each 10 mg. of riboflavin one morning, and suggested using that amount for a few weeks. The boy's nose didn't bleed that day or in the night, and as far as I know, it never bled again. He stopped having his fits of rage. Several years later his mother became chronically insane; I believe her heavy smoking, a poor diet, and an increasing hormone imbalance, were probably causing an increasingly severe energy deficiency in her brain. In that organ, as in the heart and lungs, androgenic steroids and other anti-glucocorticoids such as progesterone, are probably responsible for a normal resistance to atrophy during starvation. However, girls suffering from anorexia nervosa do sometimes have demonstrable shrinkage of the brain (which can be reversed by good nutrition) showing that the brain is not absolutely protected from catabolism, especially when the steroid hormones are out of balance.

The brain seems to be extremely resistant to the overproduction of fibrous tissue, unlike the exposed tissues of the eye and nose. There are some degenerative brain diseases, though, in which the supportive glial cells are overproduced. This may represent a basic stress-reaction, not so different from that which occurs in potato-nose and pterygium.

Although I have seen nearly instantaneous effects of a small dose of riboflavin, I want to emphasize that the enlarged and invasive blood vessels caused by a deficiency of that vitamin will not necessarily go away even with prolonged supplementation with riboflavin. I believe that the delicate red blood vessels that often first appear around the nostrils, and the larger red, purple and blue vessels that usually appear on the sides of the feet below the ankles, and more obvious varicose veins, can also result from loss of tone in the walls of the blood vessels, in addition to any overgrowth process that might be occurring, and that various problems related to stress and nutrition can be responsible. I have seen very distinct blood vessels disappear completely after using thyroid and oral DHEA. I think this is partly the result of restored muscle tone, as can sometimes be seen in the blood vessels of the hands shortly after taking progesterone.

Many people who have taken a course in physiology think that arteries and arterioles are the only blood vessels containing smooth muscles, because of the odd over-emphasis that is usually given to the contraction of arterioles. In fact, I feel that the conventional theory about the role of arterioles in regulating circulation is wrong. It is usually assumed that the capillary wall and the endothelial cells are not contractile, and this idea, with the assumption of passive veins, creates the impression that "peripheral resistance" is only the result of arteriolar tone.

Many veins are very well-supplied with smooth muscle. When the physician scoffs at the idea that varicose veins could "recover," it is because of the idea that "they occur when the valve fails." Since the valve is just a flap of tissue, it is hard to imagine how it could be restored. But if you realize that veins (especially the subcutaneous veins which become unsightly varicosities) are well-muscled, you can see that a loss of muscle tone will lead to swelling of the vein, and that a valve which could close a small channel, simply can't reach across the channel of a distended vein. That is, valve failure will necessarily follow loss of smooth muscle tone. If the tone is restored, the channel will return to its normal size, and the valve would have a chance to function again.

Although major structural restorations can occur in many tissues, even in middle-aged people, when conditions are favorable, it is much better to stop degenerative processes before they have gone very far, by optimizing all aspects of the environment, as far as this is possible.

(Synthetic riboflavin is allergenic, so natural sources are the safest.)

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Solving Some of the Problems of Aging

by Ray Peat, Ph.D.
Ray Peat's Letter

In the 1970's a strange "Pine-sol" type disinfectant with insecticide was widely promoted in Mexico, and nearly every bathroom, bus, and public room in the country smelled of that rank, un-pinelike substance. One morning I woke around 3 AM smelling Pinosol, and as I was trying to decide where the smell was coming from, I realized that I could smell it only while exhaling - it was coming from inside me. From then on, I began to wake up every night, usually between 2 and 4 AM. I knew that many old people like to get up and start their day a little before dawn, but after this experience I began to notice that many younger people have - and are disturbed by - a similar alteration of their sleep rhythm.

Around the time of my Pinosol experience (in 1979) I happened to find a dead bug in my Nescafe bottle, and it occurred to me that this was the first bug of any kind that I had seen since I arrived in Jalapa. Walking to the outskirts of the town, where there were forests, I found a reasonable number of insects, but I couldn't find one in the city. This fact, combined with my awareness that my tissues were soaked with insecticide, (and other discomforts) caused me to quit my job at the university and return to Oregon. As I was driving across the desert, I noticed that I would smell Pinosol whenever it was meal-time. Apparently low blood sugar, causing fat mobilization, would cause the insecticide to be released into my blood. I had been back in Oregon for several weeks before I quit smelling it at meal-times and in the middle of the night. But even when I couldn't smell the chemical I kept waking around 3 AM, and I got in the habit of drinking milk or orange juice to raise my blood sugar enough to lower my adrenalin (and cortisol) so that I could return to sleep.

Since I had already spent years investigating the effects of light on hormones and health, I began to see that the existing knowledge regarding the involvement of stress and glucocorticoid hormones in the aging process meshed perfectly with my concept of "winter-sickness" and the role of inadequate light in the stress-related diseases such as the premenstrual syndrome, colitis, osteoporosis, and depression.

Besides looking for the precise ways in which light acts on us (such as by preserving the function of the essential respiratory enzyme, cytochrome c), I also considered the dietary factors which might exacerbate the problem of light deficiency (such as an excess of unsaturated fats) and the possibility of other therapies, including drugs, that might be more practical and economical than hormone supplementation.

When various kinds of cells are deprived of energy (mast cells are often studied) they tend to produce (and secrete) histamine (among other substances). Unsaturated fats promote the release of histamine, while short-chain saturated fats, and glucose, inhibit it. When mice are killed by a variety of methods, they are found to have very high tissue histamine levels, so the high-histamine phenomenon seems to be about as generalized as shock. People who suffer from nocturnal asthma are known to have their highest blood level of histamine around 4 AM. Some inhibitory cells in the brain (including those involved in the "coma" state of protective inhibition) secrete acetylcholine. The similarity of the effects of histamine and acetylcholine are such that many people used to think of histamine as the "systemic cholinergic" hormone equivalent to acetylcholine. As a result of their similarity, any chemical which interferes with one of these "transmitter substances" is likely to interfere with the other, though not necessarily in the same way.

People who are awake in the dark have higher levels of cortisol than when they are asleep in the dark, that is, sleep is a partial defense against the stress of darkness. The cortisol (an adrenalin) secreted in darkness, or other stress, has the important function of maintaining the blood sugar level. The fact that cortisol causes the destruction of tissue to convert to glucose is the reason that stress and hypoglycemia are destructive. In 1971 I found that none of the sexually mature hamsters in our lab had any detectable thymus glands during the winter, though they all had them in the summer. Since estrogen and testosterone, the other thymus-shrinking hormones, are lower in the winter, I inferred that it was cortisone which caused their loss of thymus in the winter.

The main inhibitory "transmitter" substance in the brain is GABA (gamma amino butyric acid), which is closely related to aspartic and succinic acids. GABA has many anti-stress effects, besides the direct brain-quieting action. For example, it causes a sequestration of insulin, keeping some sugar from being turned into fat, and it promotes progesterone formation, which protects many systems from damaging hyperactivity.

Succinic acid was found by Szent-Györgyi to stimulate tissue respiration. Others found that it promotes the production of protective steroids, and more recently it was found to be the best material for chelating and removing aluminum from mitochondria. Succinic acid was identified as a major component of Vladimir Filatov's biogenic stimulators of tissue regeneration. Finding food sources rich in this material (especially in combination with the closely related butyric acid) would be desirable.

I experimented with various herbs known to have antihistamine and anticholinergic action, with the thought that they would help to sustain blood sugar through the night. (For example, insulin secretion is stimulated by acetylcholine from cholinergic nerves, and lowering its action during the night would decrease the need for adrenalin and cortisol.) My best results so far have been with a combination of the mildly sedative Jimson weed and the stimulant Ephedra; in combination, it seems that their antihistamine and glucose sustaining effects predominate, allowing comfortable sleep without the dry-mouth effect of their anticholinergic action.

It is now clear that both stress and an excess of the glucocorticoid hormones cause brain damage (as well as damage to all other organs). Marion Diamond's work with rats (confined or free) showed that stress causes very general brain damage, including to the cortex, and others have shown specific damage to the hypothalamus, the hippocampus, and other brain areas.[1] (Nerve cells are replaced by connective tissue cells. I think the damage is analogous to the viral (or "prionic") disease, scrapie; brain tissue from a scrapie infected young animal is antigenically similar to tissue from an old animal without the infection.)

Excessive cholinergic action in itself can cause brain damage.[2] The anticholinergic drugs, amantadine (Symmetrel) and atropine (related to the substances in Jimson weed) have been used to treat Parkinson's diseases. Atropine used to be listed as antidote for many poisons, probably because of its stabilizing effect on the nerves. It also promotes the formation of the protective hormone progesterone. Efficient energy production keeps the body from moving either to the "cholinergic" extreme or to the glucocorticoid extreme. When the mitochondria are damaged, the protective steroid pregnenolone (which is made in the mitochondria from cholesterol) can't be produced. In young people, the brain contains a very high concentration of pregnenolone and its derivatives, DHEA and progesterone, all of which stabilize cells and protect against the effects of cortisol, but in old age these fall to about 5% of their normal concentration, leaving the brain exposed to the destructive action of cortisol. The protective hormones can be used directly, or their synthesis can be promoted by using succinic acid, thyroid, vitamin A, and the atropine-type drugs, and maintaining adequate cholesterol. (T. Shimamoto, et al. have reported that low cholesterol is associated with a high incidence of stroke, especially hemorrhagic stroke.)

Since excessive excitation of cells (relative to the energy that's available) causes cells to die (in the brain, as elsewhere), it is important to consider as many of the natural means of inhibition as possible, while doing everything possible to sustain energy production. Succinic acid and butyric acid seem to be involved in both the energy sparing and the energy producing processes. The amino acids taurine and glycine are also considered to be inhibitory transmitters in the brain. Gelatin, which is extremely rich in glycine, is often added to fruit juice to take at bedtime as a sleep-supporting drink. Several of the local anesthetics including procaine and lidocaine, have cell-protecting action. Their anti-inflammatory or antihistamine function is probably caused by a more general cell-stabilizing effect. For example, lidocaine is used to prevent heart arrhythmia, and it can prevent tired heart cells from taking up too much calcium (which depletes cellular energy, in a deadly vicious circle). When taken orally at bedtime they act directly on the intestine (especially if there is inflammation anywhere in the intestine) to normalize its function, and even an occasional dose can have a long-lasting effect on the general health.

D. O. M.

The Wise One

Estrogen, too, causes brain damage. Its prenatal effect on the brain has been known for many years. Marian Diamond found that estrogen, like the stress of confinement, causes the cortex and other parts of the brain to be smaller than normal; she also found that progesterone, opposing estrogen, enlarges the cortex.

It has been suggested that estrogen's nerve-damaging action is caused by way of elevated glucocorticoid hormones. (In the "hamster lab" where I worked, other people showed that estrogen causes enlargement and hyperactivity of the adrenal cortex.)

When I first suggested that "aging is estrogenic," or that estrogen promotes aging changes, it was because of a large number of biochemical similarities in aging and in the state of estrogen dominance, and the absence of any detectable biochemical differences between the states, except their history.[3] For example, in both states the oxygen tension is relatively low, and as a result, unsaturated lipids are rapidly changed into "age pigment" or lipofuscin through lipid peroxidation.

Insomnia and hot flushes commonly occur around the time of menopause. These and other symptoms of menopause can be produced by an excess of cortisol, as in Cushing's syndrome.[4] The increase of cortisol during the night is probably responsible for "night sweats." When progesterone is deficient, cortisol - even in "normal" amounts - has a stronger effect.

The animal evidence is now clear, showing that it is largely the prolonged exposure to estrogen which causes reproductive aging.[5] Treatment with progesterone can prolong fertility,[3,6] as well as controlling symptoms such as insomnia and osteoporosis.

Until we know how to modify the environment (especially the radiant spectrum in the region of 600 nm to 1200 nm) to minimize the stress of winter and nighttime, the use of nutrition and hormone balancing techniques can control symptoms and minimize the cumulative damage that is occurring while we have the symptoms.

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For subscriptions to Ray Peat's Letter please inquire at 3997 Dillard Rd., Eugene, OR 97405. ◆

Sales Pitch for Linseed Oil

Editor:

Your publication performs an important service in allowing the free expression of ideas in medicine and related subjects. Many publications, contrary to the spirit of science, "protect" their readers from improper ideas. Too many publications are actually protecting their advertising revenue by rejecting criticism of certain drugs or food supplements. Industries with annual profits in the billions of dollars have the power to control medical journals, professors of medicine, and public opinion. *TLfD* is one of the few publications which has allowed criticism of the idea that our diet should be supplemented with the essential fatty acids.

The article in your December issue by Mike Minarsich, and the book review excerpt by J.S. Bland, Ph.D. call for some special criticism. Minarsich is obviously a linseed oil salesman (president of New Dimensions Distributors), and he takes his pseudo-facts right out of the book by Udo Erasmus, so my comments are mainly about the Erasmus book, and some of its ideas which are derived from the "scientific work" of Johanna Budwig.

Dr. Bland's review excerpt says "*Fats and Oils* is filled with interesting and accurate information..." and "is the first complete guide to *everything* you need to know about fats, oils and cholesterol to make the right food choices for your health." T.H. Huxley said that book reviewers too often get all their information on the subject from the book being reviewed, like the Abyssinian who supposedly took his steaks from the same ox he was riding; but it is hard for me to believe that Bland has really read this error-filled, incompetent, and possibly deliberately misleading book. If Udo Erasmus is a hired commercial writer working from information provided by his employer, then he has done a smoothly competent writing job, and it is the publisher who misleads by failing to give some background information. Judging by the book, I suspect that neither Erasmus nor Budwig has studied the fundamentals of organic chemistry. That isn't important. But it is very important that linoleic acid, and related oils, in the amounts recommended by Udo Erasmus, are known to cause:

impaired brain development and learning;
damage to skin and bones;
accelerated aging and age-pigment accumulation;
damage to the circulatory system;
increased cancer incidence;
suppressed immunity;
endocrine dysfunction.

U.S. consumption of seed oils had been almost doubling every decade since the first world war, but the technological advances of the 1960s which allowed paints to be made from petroleum derivatives, rather than from linseed oil, safflower and soy oil, stimulated the redirection of large amounts of these substances from paint production into the food market. Clever marketing tricks are in some cases creating price mark-ups of 10,000%. I spoke to a dealer who said he recognized the toxicity of linseed oil and wouldn't use it himself, but that the profit was so big he was going to keep selling it.

An acquaintance who died recently after several months of eating large amounts of linseed oil told me that it had been used by both W.F. Koch, M.D. and Max Gerson, M.D. I knew this wasn't true: For example, Gerson's program evolved from a diet for migraine and tuberculosis into a cancer therapy, and involved the use of thyroid extract, liver, fresh juices, and a little butter, but over and over he said "absolutely no oil." My friend sent me a page from Gerson's book, containing the recommendation for 1 tablespoon of linseed oil. My copy of the Gerson book, published while he was alive, contains no such statement on that page, but rather the phrase in bold capital letters, NO OILS! My informant also assured me that Gerson had known Budwig and respected her work. Gerson's book contains detailed discussions of all the main dietary approaches to cancer, with a large number of references to the scientific literature, and it did not mention Budwig at all. Since Budwig's proposals are diametrically opposed to Gerson's he would have had to account for them if he had known of them.

The people who are using Max Gerson's name and reputation to sell linseed oil are harming the people they mislead, and are dishonoring Gerson's important work. The altered book is going to boggle the mind of any thoughtful student who tries to understand what Gerson was really doing.

Minarsich and Erasmus similarly invoke the names of several great biochemists in making their sales pitch for linseed oil. Any serious student of biochemistry will recognize the absurdity of their outline of biochemistry, but the average reader is likely to swallow the idea that Ms. Budwig represents the culmination of a century of scientific progress. Dale Alexander made a career of the idea that cod liver oil will grease arthritic joints. Now a generation

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later, the vast food oil industry has a slightly higher class of sales promoters. It is urgent that we start developing a more critical medical-scientific culture.

Research showing the toxic effects of unsaturated oils goes back more than 60 years. A 1985 article published in my newsletter cites some of the key references. These substances inhibit many enzymes (e.g., in digestion, in immunity, in clot removal, in thyroid function), they disrupt mitochondrial energy production, and they interfere with communication between cells. We hear very little about these toxic effects, and there is not much money available for more research in these areas. Naturally, these topics aren't mentioned in the Erasmus book. The "toxicity" questions treated in the book do not include the toxicity of fresh and natural unsaturated oils, and so they have the function of a red herring, distracting the reader.

For nearly 20 years, mainline medicine has advocated the use of unsaturated oils "to protect the heart." A few scientists, like Hans Selye, kept telling the (contrary) truth. Now big business has many people in "alternative medicine" falling for the false establishment story.

Reference:

Ray Peat's Newsletter, "Interactive Toxicities of Unsaturated Oils and Iron," 1985, 41.

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Streptococcus Faecium Not Faecalis

Editor:

Here are some comments concerning acidophilus products and *L. acidophilus*.

We believe that it is true that acidophilus products for human use were, in the past, mostly *Lactobacillus casei*, ssp. *rhamnosus*, especially in European countries. Today, a large percentage of products of lactic bacteria for human use contain two or more species of lactobacilli, bifidobacteria and streptococci. That is the result of newer knowledge of the lactic flora of the intestinal tract. It is now known that normal intestinal flora contains, per gram of feces, billions of bifidobacteria and millions of lactobacilli and streptococci.

Most important species of bifidobacteria found in the intestinal tract are *Bifidobacterium infantis, B. adolescentis, B. longum, B. brevis* and *B. bifidum*. Lactobacilli include mainly *Lactobacillus casei*, ssp. *rhamnosus, L. fermentum, L. acidophilus* and *L. salivarius*. *L. bulgaricus* and *L. lactis* are not adapted to intestinal conditions. They may be found in the intestinal tract when they are regularly ingested in large amount. That is the case of *L. bulgaricus* for yogurt consumers. However, the survival does not exceed 7 to 10 days after heavy and prolonged consumption. Lactic streptococci, especially *S. faecium* and *S. thermophilus*, are normal and highly beneficial inhabitants of the intestines. *S. faecium* is most important for the colonization of the intestinal mucosa, assuring protection of the organism against infection by harmful microorganisms.

Rosell Institute, Inc., the "Montreal-based bulk dairy culture producer," was incorporated in 1934. It was founded by three professors of OKA Agricultural Institute: Dr. J.M. Rosell, Dr. G. Toupin and myself. Rosell Institute Inc. is a Microbiological Institution specializing in the production of microorganisms for the food industry, soil fertilization, human and animal prophylaxis and therapeutics. Its technology and teachings have followed scientific developments.

One of the numerous species of lactobacilli produced by Rosell Institute for human use is *Lactobacillus casei*, ssp. *rhamnosus*. L. rhamnosus is very different from L. casei. Differences concern morphology, physiological characteristics, antibiotic activities and immunological properties. Some strains of L. casei are well adapted to cheese aging. L. rhamnosus is probably the most important species of lactobacilli. It is well adapted to intestinal conditions, has good activity against harmful microbes and contributes to development of immunity. Moreover, it is much more potent, prolific, ubiquitous and efficient than L. acidophilus.

From 1910 to about 1970, lactobacilli isolated from feces or intestinal tract were generally called *Lactobacillus acidophilus*. That name was applied to lactobacilli from intestinal origin used for experimentation with humans and animals. Experimental reports very seldom mention full identity of the concerned lactobacilli. The results were attributed to *L. acidophilus*. How often was it true? When practical and extensive identity tests were available, it appeared that *Lactobacillus acidophilus* products contained almost exclusively *Lactobacillus rhamnosus*. That was the situation in Europe and America. A few products contained *L. fermentum;* one product contained *L. acidophilus*.

Storage Conditions

All species of lactic bacteria have longer life and better stability at low temperature. Our tests on lactobacilli and bifidobacteria, extended over some decades, have shown an average monthly decrease in the number of living cells of 1% under freezing conditions, 2% under refrigeration and 5% at room temperature. These data concern only freeze-dried cultures. Cells of *Streptococcus faecium* are three to four times more resistant than those of lactobacilli and bifidobacteria. Consequently, it is important to store lactic cultures at low temperatures as much as possible.

Good stability requires also low moisture content. Lactic cultures must be packed in air and moisture-proof containers.

Mix of microorganisms

In the intestinal tract, there is naturally a mixture of several species of lactobacilli, bifidobacteria and lactic streptococci under normal conditions. For several reasons, such normal flora may be partially or almost completely destroyed. It is then very important to re-implant or re-establish that flora for the protection of the organism and prevention of putrefaction and toxicity.

Though one adequate species of lactic bacteria, adapted to intestinal conditions, may be highly beneficial it is more logical to consume several species, provided they grow well together and do not show incompatibility or antibiosis. Aerobic lactobacilli will help anaerobic bifidobacteria by creating better growth conditions and each species may contribute to better nutrition of the whole population. There is such a thing as symbiosis and synergism.

Rosell Institute produces and freeze-dries all the important species of lactobacilli, bifidobacteria and lactic streptococci. It cooperates with nutritionists, doctors and distributors of Health Products to inform them properly and supply them with the mixtures of lactic bacteria that they wish for their specific needs.

"Something dophilus"

It is true that several companies use the word "dophilus" in their brand names.

Supplement Safety

by Ray Peat

Around 1976, there were some warnings about the occurrence of kidney and breast cancers from prolonged use of reserpine, which had been very popular for controlling blood pressure. It was thought that the elevation of prolactin by reserpine accounted for the production of tumors. Since tryptophan stimulates prolactin secretions, I thought it might turn out to be just as carcinogenic as reserpine. The people who sell tryptophan don't want to hear this.

Olney's work in the 1970's with aspartic and glutamic acid should have aroused the public to be cautious about the use of isolated amino acids. Even after these amino acids were shown to cause seizures, many companies continued to sell them without warnings.

Orotic acid was known to alter pyrimidine and ammonia metabolism, so I thought it wasn't wise to use supplements that contained large amounts of it. A couple of years ago orotic acid was described as "an excellent liver carcinogen," based on experiments with rats. I have known people who used it regularly in quantities similar to those which are carcinogenic for rats. But it continues to be sold, without warnings.

In 1953, a few small tablets of ascorbic acid completely cured my posion oak and I never got it again though I worked in the woods every summer for several years. But in the late 1950s, I had cold-like symtoms for a few days after I took a 500 mg. tablet, and the same thing happened when I took another tablet a few months later. In the late 1960s, I began taking ascorbic acid regularly and I had a chronic cough; about a year later, I developed bleeding colitis. These symptoms stopped when I stopped taking ascorbic acid. I found that I could detect a very small amount of synthetic ascorbic acid in processed foods, by the recurrence of those symptoms. Over the years, seeing other people with similar symptoms, I would tell them about the allergenicity of vitamin tablets or powders, and their symptoms would go away. In this way I saw that the most frequent sensitivity was to ascorbic acid, riboflavin, and rutin. Later, I learned that these are synthesized from cornstarch. Synthetic ascorbic acid contains significant amounts of heavy metals, apparently introduced by the use of sulphuric acid as an oxidant. (The manufacture of sulphuric acid has customarily involved the use of a "lead room." I don't know whether this technology is still in use.) I experimented with large daily intakes of vitamin C, for example 4000 mg. per day in the form of fresh grapefruit juice, and didn't experience any unpleasant reaction, but 1 or 2 mg. of the synthetic form – taken by accident in foods such as all-bran breakfast cereal, bread, or sausage, which I didn't suspect would contain added ascorbic acid – would cause days of sickness with intestinal bleeding. Since my reactions to metabisulfite and to synthetic ascorbic acid are similar, though not identical, I suspect that sulfur compounds produced in manufacturing ascorbic acid are partly responsible for its allergenicity. Interestingly, I have had strong allergic reactions to several kinds of single amino acids; I suspect that these, and many other foods and supplements, are exposed to sulfites or ascrobic acid that have been used as preservatives at some stage of manufacture.

Although more people are writing about the dangers of iron supplementation now than when I wrote about it in *Nutrition for Women* in 1975, it seems that people are using just as much as ever. A hundred years ago, arsenic was the common treatment for "anemia," and it "worked," just as iron works to raise the production of red blood cells. This "anti-anemia" effect is a reaction to injury, and has nothing to do with a nutritional iron deficiency. Even heavy menstruation involves the loss of only 30 or 40 mg. of iron per month, or about 1 mg. per day, and it is practically impossible to get such a small amount in the diet. Immunosuppression and carcinogenesis by iron have been well established for about 20 years.

Substance Abuse

The Center for Science in the Public Interest got a lot of publicity a few years ago when it petitioned the FDA to require warning labels on products that contain caffeine. Many other groups circulate warnings about the "dangers" of coffee. When coffee was introduced into Europe, some people seemed to think it was an evil witch's brew; Bach's Coffee Cantata ridiculed the great fear of coffee.

To make false claims about anything abuses the truth. A network of mistaken beliefs can lead to a perverted culture, which ignores important issues because of ➤

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Supplement Safety

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an obsession with false issues. I think it is useful now and then to outline the kinds of mistakes that are being made regarding the abused substances, coffee and caffeine.

Dr. Minton at Ohio State, and the mass media which mindlessly echoed his beliefs, started a cultish idea that caffeine caused cystic breast disease. His publications are marvels of ignorance and irrationality, which probably someday will be used in college classes to illustrate America's blind faith in the cult of medicine. Other studies found an entire lack of association between caffeine and breast disease, but I will not be surprised if caffeine is ultimately found to be therapeutic for some types of cystic breast disease, because of its effects on hormones and cell-regulation.

Decaffeinated coffee was found to be associated with cancer of the pancreas. A residue of solvent in the coffee is a likely candidate for explaining the association, since the other groups found by epidemiologists to have a high rate of pancreatic cancer were people who work in gasoline stations and in dry-cleaning businesses. Several studies have found caffeine to have a protective effect against cancer. For example, Würzner, *et al.* found that tumor incidence in rats fed coffee went down as the caffeine content went up ("A two-year feeding study of instant coffees in rats. II. Incidence and types of neoplasms," *Food Cosmet. Toxicol.* 15:289-296, 1977).

Caffeine has several effects which protect against cancer. It strongly protects against the cancers caused by chemical carcinogens (including those in smoke), and even against those caused by ultraviolet radiation. It stimulates the repair process which corrects mutations (in mammals, but not in bacteria), and it stimulates the immune system.

I think some of the beneficial effects of caffeine result from its stimulation of the thyroid gland, and of normal respiration. While it stimulates normal respiration it has an anti-inflammatory action, which probably involves both prostaglandin regulation and an antioxidant action. It is chemically very similar to our natural antioxidant, uric acid, and it raises the level of uric acid in both the blood and the urine.

Giving rats the human equivalent dose of 3500 mg/day has no harmful effects, even when continued for several generations. One study found no harmful effects when rats were fed large amounts of caffeine for up to three and a half years. Since lab rats rarely live that long, I think caffeine's effects on longevity should be investigated.

Theophylline, found in tea, is very similar to caffeine. It has been shown experimentally to retard the growth of cancer cells, and even to promote their recovery of normal function It is widely used to treat asthma. Theophylline and caffeine have been used to treat apnea in infants, since they stimulate the nerves that regulate breathing. Many people who use theophylline for their asthma don't realize that a few cups of tea would provide the same drug, more pleasantly and less expensively.

Dietitians and their textbooks generally suffer from a cultish belief that coffee and tea "have absolutely no nutritional value." The British found that tea and coffee provide about 20% of their national dietary intake of several essential nutrients. When the complete absence of certain essential nutrients in white bread was discussed, dietitians defended the use of white bread as an appropriate part of a balanced diet. I mention this simply to establish the cultish nature of their professional behavior, not to advocate the use of whole grains or a larger consumption of tea.

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Medical Director's Newsletter

Number 4, Winter 1989
Published by Blue Cross of Washington and Alaska
Seattle, Washington 98111

Nystatin and Systemic Candidiasis

This prescription drug is specific for vaginal, intestinal or oral candidiasis. We do not recognize systemic candidiasis as a diagnosis without definitive test results which support the diagnosis.

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Other tests *may be suggested* depending on the particular circumstances of each case such as allergy testing (vitamins, foods, environmentals, etc.), pH titration (to determine level of stomach acidity function), or anything else that is appropriate.

III. Diet and Supplementation: Supervised dietary supplementation is based on test results and supervised dietary counseling. The patient is asked to schedule an hour visit with a view to advise supplementation a minimum of 72 hours (optimal 1-2 weeks) prior to the dental appointment which involves actual removal of amalgam materials.

IV. The Dental Referral: If the patient has not already contacted a dentist, we shall provide a source list of area dentists who provide sequential removal of amalgams, safety procedures with respect to mercury in the dental office (air filtering system, rubber dam, etc.), and replacement with biocompatible materials, etc. All efforts are made to then coordinate the medical care with the dental work that is to be undertaken such as the Dental Amalgam I.V. with EDTA and vitamin C within two hours of each dental appointment for protection against release of mercury vapor during procedures. The I.V. may be administered prior to the amalgam removal with deletion of all vitamin C to avoid the interference known to occur with the anesthetic. After dental amalgam removal procedures, the vitamin C - I.V. or oral vitamin C supplements - may be taken immediately.

V. Office visit follow-up one week after amalgam removal. This may be a phone consultation.

VI. Office visit or phone consultation follow-up two weeks after amalgam removal.

VII. Follow-up blood tests at three weeks include CBC with differential and chemistry profile, along with urine mercury.

VIII. Follow-up blood tests at three months, post-amalgam removal, include CBC with differential, chemistry profile and urine mercury, along with a hair trace mineral analysis.

IX. Follow-up at six months will include a CBC with differential and chemistry profile, as well as urine mercury and hair trace mineral analysis.

All of the aforementioned procedures should be followed to the letter in order to obtain the best results from amalgam removal. Patients have been harmed by neglect of any one of these important phases. Do not take short cuts.

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Sharks, Salmon & Osmotic Therapies

Editor:

In the 1960s, I met Leonell Strong, the geneticist who developed a famous strain of mice that are extremely susceptible to breast cancer. My first research in endocrinology had to do with their estrogen metabolism, and ways to normalize it. Strong (who studied genetics with T.H. Morgan) was interested in the fact that sharks are not susceptible to cancer. As a geneticist, he saw this in relation to their "genetic stability," that is, the fact that they haven't developed beyond an early stage of evolution, and he believed that cancer is a result of genetic instability. He found that injections of an extract of shark's liver prevented mice from developing breast cancer; however, similar extracts from other kinds of liver had similar effects on the mice. Since his mice had too much estrogen, I supposed that their livers were deficient in something needed to eliminate estrogen, since the liver normally is a powerful regulator of estrogen, using a certain system of "detoxifying" enzymes. (As it turns out, the thyroid hormone is the basic regulator of this detoxifying function.)

As I studied estrogen in other situations, two features of its action stood out - it interferes with respiration, and it causes cells to take up water. Its other effects seem to follow from these. In the 1920s, it was found that hypotonicity, an excess of water, stimulates cell division (while hypertonicity inhibits it). Around 1940, Hans Selye found that estrogen's systemic effect mimics the shock phase of the stress reaction. In shock, deficient circulation of blood and thus deficient oxygenation of tissue are the main problem, and Selye considered the adrenal steroids to be crucial in resolving the problem, and creating adaptation to the stress. But the adrenal steroids can have their own undesirable consequences.

Sharks, besides being primitive and not suffering from cancer, are physiologically unique in another way: their body fluids are osmotically in balance with seawater, making them hypertonic to other animals' body fluids. The mineral content of sharks' blood is not very different from that of other animals. The osmotic difference is made up by a very high concentration of urea (and of trimethyl ammonium). In general, animals that live in water are able to get rid of ammonia easily, because it is very soluble in water, and the excretion of nitrogen as urea and uric acid is considered to have evolved to avoid the toxicity of the large amount of ammonia that would otherwise accumulate in land animals. Therefore, it seems that sharks' urea evolved as a kind of osmotic buffer (rather than as an excretory product), keeping them in osmotic balance with ocean water, without having to deal with internalization of the extremely high (3.3%) sodium content of ocean water.

Another kind of fish, the salmon, which return to fresh water for reproducing, show the other extreme of adaptation to an osmotic problem. After living "isotonically" in the hypertonic ocean environment, keeping their mineral content and osmolarity lower than sea-water's, they suddenly have to readapt to the extremely hypotonic fresh water. The secretion of prolactin and glucocorticoid steroids seems to facilitate this sudden adaptation, but those hormones also seem to produce an explosively rapid kind of aging. I think their condition is similar to the "Cushingoid" symptoms that frequently appear in middle-aged people.

Highly energized cells can resist the osmotic stress of too much water in their environment, and tired cells can't. Removing the stress, by making the surrounding fluid isotonic or slightly hypertonic, can protect the cells' energy level, and give them a rest. Until about 1940, the use of hypertonic solutions in therapy was fairly common. Books still mention the use of urea, USP, as a diuretic to treat brain swelling, but I haven't heard that it is still used this way in the United States. Veterinarians sometimes use hypertonic urea to treat uterine inflammation and infected wounds. Early in this century it was often mentioned as a safe disinfectant and promoter of healing

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for wounds. It was sometimes used as a powder, and was sprinkled pure onto skin grafts or between bone fragments in repairing fractures. Although it caused some pain, people generally thought it accelerated healing while preventing infection. (Typically, 5 grams of powder would be closed into the wound; milder treatments would probably have been possible, but wartime conditions didn't foster subtlety in medical research.) (Symmers, *Lancet,* December 4, 1915.)

Hypertonic sodium chloride (Clifford White, *Lancet,* October 30, 1915) was also used to treat infected wounds, and its success in treating war wounds led to its use as a vaginal douche in treating various inflammations and infections, including infections associated with child-birth, salpingitis, cellulitis, gonorrhea, vaginitis, and erosions of the cervix, and in preparing a cancerous cervix for surgery. Irrigation of the abdomen with the saline solution gave good results in acute infections that required abdominal drainage. White used a solution containing 1/2 ounce of sodium chloride and 1/16 ounce of sodium citrate in a pint of water. M. Englaender (*Med. Klin.* January 2, 1916) used intravenous injections of 100 ml. of 2% NaCl to treat a variety of infections and inflammations.

In Russia, Gubin (*Russky Vrach 14*(38)) treated sciatica with two glasses of warm water containing 1.4 teaspoonfuls of NaCl, placed in the rectum; it caused profuse sweating and diuresis.

I have known many people with food allergies (or with lingering cold or flu symptoms) who said that although their abdomens were distended and uncomfortable, they were so thoroughly constipated that no laxatives worked. When their bowels did move, they sometimes described ribbon-shaped feces. Occasionally I saw their X-rays, in which an opaque "meal" showed up as a very thin and intermittent filament. It appeared that the wall of the bowel was enormously swollen. One woman complained that enemas were useless, because when a quart of water was injected, nothing returned from the bowel, though she would have to urinate more than usual. The colon was obviously drinking the water. I suggested that she try a hypertonic glucose and salt enema, with an aspirin added, neutralized by a little soda, and she immediately had good results.

People with less complete obstruction can get the same effect by drinking a hypertonic solution of epsom salts and sodium chloride, with an aspirin. Although this osmotic deflation of inflamed tissue is crude, I think it helps to promote real recovery, by reducing the reactivity of the tissue, and allowing it to recover its normal energy patterns.

In PMS, edema is a common problem, and it used to be thought that edema of the brain was responsible for the irritability or depression or other nervous symptoms, and diuretics such as ammonium compounds and urea were commonly used. (Premenstrual salt cravings are the result of the estrogen-disturbed water balance, and salt-restriction for PMS is as inappropriate as it is for pre-eclampsia or toxemia of pregnancy.) Alkaloids are often active in modifying the water content of physical systems, as well as of cells. The alkaloids that are often used in treating PMS seem to favor improved oxygenation and elimination of edema. I suspect that these drugs, and the natural hormones progesterone and pregnenolone, act in the same direction as hyperosmolarity.

For several years, I have been interested in the biological effects of ammonia, and compounds that are metabolically close to it. There is clear evidence of ammonia's antiviral effect, which stimulated extensive research by drug companies seeking patentable antiviral amines. Most simple substances have regulatory functions in themselves, besides participating in other systems. Besides viral immunity, I think ammonia is involved in regeneration and nerve modulation. Urea, inosine, GABA, the polyamines, and betaine derivatives (e.g., gamma-butyrobetaine) are closely related to ammonia metabolism, and combinations of them will probably have many useful biological effects.

Sodium chloride, glucose, and other substances can be used at high concentrations for their osmotic effects, but they also have chemical and metabolic effects that aren't necessarily desirable. Both osmotic and biochemical effects should be taken into account in a given therapy.

Ray Peat, Ph.D.
Ray Peat's Newsletter
P.O. Box 3427
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Homeopathy vs Allopathy

Editor:

We would like to thank Dr. Saul Pilar of Vancouver, B.C. for his thoughtful and informative discussion, "What Healed Sarah?" We appreciate and welcome feedback and discussion stimulated by our articles. There was a great deal of improvement when Sarah was given the remedy, Calcarea carbonica, as well as improvement in laboratory values. Indeed, whenever Sarah has relapsed, the remedy once again allows her enough energy to function, enables her to lose weight, stops hair loss and helps her think clearly again. This does not occur until she gets the remedy, which stimulates rapid improvement in her symptoms. Her hypothyroidism has not resolved on its own, but continues to be improved under continued homeopathic treatment, without the need for Synthroid.

We agree that it is important not to attribute success to a treatment, homeopathic or allopathic, when the body would have done the same healing without it. But let's not ignore the effects of a treatment which has produced obvious improvement, subjective and objective, just because some patients have improved without it in the natural course of their healing process.

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Letters to the Editor

Correction Notice

Editor:

I am writing to call your attention to an error on page 687 of the December issue of *Townsend Letter for Doctors*, in the article on scleroderma. The dosage of DMSO for the rheumatoid diseases is 0.5 - 1.0 cc DMSO per kilogram of body weight, not grams per kilo. The DMSO used was Rimso 50, which is 50% DMSO. The article is otherwise correct.

The patient was last seen in my office in October 1987 and she is continuing to improve. Dr. Thompson at Texas Kidney Institute is very pleased with the patient's outcome, and only sees her yearly now. Lab studies done there in early November '89, were Creat. Clear. 50, Serum Creat. 2.1, she is still on BP medicine, but nothing else.

Sorry for the error, although I doubt that there will be any problem as this is a very safe medication. I will be glad to help anyone who wishes to use this therapy, to see if they can get the same results.

Keep up your good work with the newsletter.

Ronald M. Davis, M.D.
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Peat's Position on Non-Essentiality of Fatty Acids is Unwarranted

Editor:

The recent point-counterpoint on essential fatty acids by Peat and Levin (#77, Dec. 1989) deserves comment, in case anybody is paying attention. Peat seriously misrepresents the literature on the subject when he tries to show that the essential fatty acids (EFA's) are not essential. There are no experts in the field who now disagree on the essentiality of the ω-6 family in man and lower animals while the independent essentiality of the ω-3 EFA family is established although the clinical effects of its deficiency are still being investigated. For this author to cite only two selected references on this matter, taken from the 1940's and 50's, in the face of the vast literature built up during the past half century of modern biochemistry and clinical investigation is inexcusable. Those who do not read (or understand) the literature are condemned to repeat it.

From this unwarranted position, Peat naturally has nowhere to go but to consider toxic effects and come to the conclusion that the EFA should not be consumed at all. The public and clinician alike would be well advised to disregard this advice until Peat has placed himself and his family on an EFA free diet for, say, two years. In fact, my own recent studies, both theoretical and clinical (Rudin, D.O. and Felix, C., *The Omega-3 Phenomenon*, Rawson-Macmillan, 1987; Avon, paper, 1988), show that there is a serious deficiency of the ω-3 family from refining and other factors and that this can be related to a widespread synergistic malnutrition involving deficiencies of dietary fiber and other essential nutrients along with excess consumption of adversely interacting co-nutrients, such as saturated and 'funny' (isomeric) fats, all of which may account for the *modernization disease syndrome* now comprising the bulk of illnesses which medical epidemiological studies have shown to be unique to dietarily modernized societies.

Of course, too much of a good thing can be harmful and the issue, as always, is one of optimization. But to condemn consuming an essential nutrient in the face of its deficiency is untenable.

This article is a good example of why reputable journals require expert editorial evaluation before publication, especially if the issues are controversial and presume to be on the leading edge of knowledge.

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Review Needed on Source, Extraction and Storage of Fatty Acids

Editor:

Health has been a necessity for me since my recovery from environmental sensitivities and came largely as a result of my own efforts. It was through the search for answers that I came to know Stephen Levine [Nutri-Cology] whose research has helped me greatly.

Of special interest in your December 1986 issue was the article on "The Complicated Patient" by Sidney Baker and Leo Galland. More recently Leo Galland has written on the importance of treating parasitic infections. These are brilliant men in their field and it is the publication of articles such as those that makes the *Townsend Letter* exceptional.

In the future, I would like to see material on the research of Johanna Budwig. Her work with fatty acids has been ignored far too long. It would also be a service to your readers if you were to publish material on the importance of the source, extraction and safe storage of fatty acids. Johanna, in her recent letter, referred to the work of Udo Urasmus. Udo has written an excellent book on the subject entitled *Fats and Oils*. Anyone interested in fatty acids should not be without this excellent reference.

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Effect of Linseed Oil on Platelet Adhesion

Editor:

There has been much in these pages of late about linseed oil, pro and con, but no mention has been made of its effect on platelet adhesion and the prevention of death from thrombosis and myocardial infarction (MI). Late in 1965 I initiated a research project at the National Heart Hospital in London, England that was to take six years and at a cost of over $250,000 on the feeding to cardiac patients one sweet roll each day that contained 15 ml. of linseed oil.

As background, in late 1965 I met Paul Owren, Professor of Hematology at the University of Oslo in New York City. He had had a most exciting paper in the August 1965 issue of the *Annals of Internal Medicine* (pp167-175). In it he had reviewed the connection between diet and heart attack deaths in Norway during German occupation in the years 1940-1945 and in the ten post-war years. In these pages

Circumcision

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discourage circumcision and to refuse to perform it.

Physicians today have a unique historic opportunity to correct the mistakes of the past by realigning medical practice with ethics and the principles of human rights. Every individual has a right to the body he or she was born with. Physicians have a duty to protect this right and to uphold the first tenet of the Hippocratic oath "First, Do No Harm."

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Preserving the Tissues

Osteoporosis and the Skin

by Ray Peat, PhD

While I was working on my dissertation, around 1970, the opposition between stress-injury and energetic resistance became increasingly apparent to me. Estrogen (like X-irradiation, aging, or trauma) called up the cortisone response, and other factors, especially progesterone and thyroid, and allowed the organism to restore itself in ways that neutralized the cortisone response. Therefore, when I saw that the estrogen-like processes became more and more dominant after middle-age, it was natural to think of progesterone and thyroid as the main factors that should be replaced. This is why in 1975 I described menopause as resembling Cushing's syndrome, which is caused by a toxic excess of cortisol. Osteoporosis, hot flashes, insomnia, and mood disorders are caused by cortisol, and so I tried using progesterone and thyroid – the anticortisol factors – for those conditions. The results were so profound that I began to study the general implications for health, and to try to understand the mechanisms so that prevention might replace treatment.

Several people who had been abandoned as hopeless terminal cases – with "epileptic brain damage," inflammatory degeneration of hip and thigh bones, diabetic gangrene, senility – recovered their health within a few days, and went on with their lives in productive and pleasant ways.

I knew that intense and frequent epileptic seizures cause the exhaustion and death of brain cells. A 52 year-old woman had been having seizures for over 15 years. Her neurologist gave her a mental exam every year, and considered her to be hopelessly demented. After using progesterone for a few days, she functioned normally. After about a year, she returned to graduate school at the University of Oregon, and got a master's degree with straight A's.

A 79 year-old woman had had artificial hip joints implanted when she was in her fifties, but her bones had weakened to the point that no further surgical repair was possible. She settled her affairs, and didn't expect to get out of bed again. After using progesterone topically and orally, after two weeks she was able to get out of bed and return to her normal activities. At the age of 85, she went camping on the beach in Mexico, and travelled to Scotland.

An 82-year old man was agitated and confused, and was apparently suffering from senile dementia. After being given progesterone and pregnenolone for a few days, his mind became clear, and he returned to work on scientific projects he had begun decades earlier. A squamous cell cancer on his lip regressed, and never bothered him again.

A 60 year-old woman had "osteoporosis" (shrinking) of the jaw bone that was causing her teeth to loosen. After applying progesterone solution to her gums daily for a few months, her teeth became firm.

When bones had almost disappeared from X-rays, yet became firm and functional within a few weeks, it was obvious that regeneration had taken place. But when brains went in a very short time, from imbecility or idiocy to intellectual productivity, I could only guess what might be happening to the cells. But I got a useful perspective on the mechanism of progesterone's action by seeing some recoveries that were even faster than those I have mentioned.

In animal experiments, I knew that estrogen causes cells to take up water within a few minutes after it reaches the tissue, and that this is at least partly the result of its interfering with the availability of oxygen. Within 40 minutes of administering a large dose of estrogen, the lungs become extremely inefficient at oxygenating the blood. This involves a sudden thickening of the alveolar membranes and the walls of capillaries, simply by taking up water. So, when I saw bulging veins disappear a few minutes after women took progesterone, along with a sudden lifting of extreme depression, I guessed that their circulation had become more efficient, and that better oxygenation had changed their mood.

Then, I repeatedly saw physical changes in other people that were visible

within an hour, and that involved a sudden movement of water out of edematous tissues. In many people with damaged joint cartilage (confirmed by various types of examination, including arthroscopy), the joints became mobile in an hour, and by the next day, the defect no longer existed. A man who was purple from emphysema changed color within a few hours, and within a few days was going to work. The bulging eyes of exophthalmic Graves' disease receded into their sockets noticeably within an hour, and were normal the next day. Simply increasing the circulation couldn't have done those things. Opposing estrogen's edema-promoting action was involved, but I couldn't imagine any mechanism that could explain such rapid movement of water from the swollen tissue into the bloodstream.

One of estrogen's effects is to lower the amount of albumin in the blood. Estrogen causes the liver to synthesize less albumin, partly by causing the messenger RNA to be destabilized and degraded. (Iron can have some similar effects on liver RNA.) When there isn't enough albumin in the blood, water moves from the blood into the tissues, causing edema. (Premenstrually, edema might seem to be just a nuisance, but it can eventually become a serious problem, with aging or pregnancy, for example.) Albumin binds oily substances, and its conformation seems to be opened when it binds them. Progesterone is known to adsorb strongly to proteins – it has been called a "cardinal adsorbant," meaning that it can bind in ways that cause the protein's adsorptive capacity to change. I believe that progesterone and pregnenolone oppose estrogen in many ways, but the amazing speed with which they can cause major structural changes in the soft tissues convinces me that one of their first sites of action is the albumin molecule, causing its conformation to open in such a way that it is able to more strongly bind water molecules. This physical change in albumin would change the blood's osmotic/oncotic pressure, causing water to flow into capillaries. As the edema is reduced, oxygenation is more efficient, because the pathway for oxygen diffusion becomes shorter.

Albumin has been described as a first line of defense against toxins, since it binds them until the liver is able to degrade them chemically. Progesterone, pregnenolone, and cholesterol are known to increase the organism's resistance to a great variety of toxins. (Selye coined the name "catatoxic steroids" to describe steroids of this type.) If these steroids bind to albumin in a way that opens the protein to increase its binding capacity, that single process could explain the "catatoxic" effect, as well as the anti-edema effect.

When the blood is unable to retain its normal amount of water because of insufficient albumin/sodium, the blood volume is reduced as the tissues become water-logged. This causes the hematocrit (the proportion of cells in a volume of blood) to rise, and this increased packing of red blood cells causes the blood to become more viscous. (Knisely studied this phenomenon in a great variety of sicknesses.) Increased viscosity and slower flow decrease the blood's ability to deliver oxygen and nutrients to the tissues, including the blood vessel walls, modifying their tone. Slower flow, even without any changes in the fibrin fibrinogen system itself, increases the formation of clots.

This description of progesterone's immediate action is intended to take some of the mystery out of its dramatic effects, but it isn't intended to argue against any of its actions within cells. It serves to give a general picture of how progesterone can systematically reduce stress and its harmful consequences, just by making blood circulation more efficient.

At first I most often used progesterone dissolved in olive oil to stop the stress-induced processes of deterioration, with a high protein diet to support the processes of repair. Now, I have added a variety of other techniques.

There always seems to be a rough balance between tissue regeneration and tissue degeneration, with growth and repair occurring when the equilibrium shifts in one direction, and with atrophy or degeneration occurring when the balance shifts in the other direction. If we can understand the mechanisms of atrophy, and how to retard or to block tissue destruction, then we can restore the balance to a degree which might allow regeneration to occur, even if we don't clearly understand the mechanisms of growth.

Skin and bones are such different types of tissue that it will be useful to start with them, because if we can see similar processes of degeneration or regeneration in them, then the chances are good that the same processes will occur in other tissues too. Bone is a relatively stable tissue, while skin is a tissue whose cells divide rapidly.

It is common medical knowledge that cortisone and related glucocorticoid-type hormones cause skin to atrophy, becoming thinner. Using topical applications of a synthetic derivative of cortisone, C. M. Papa and A M. Kligman showed that the atrophy extended to the pigment cells, reducing their size and eliminating most of their dendritic branches. They also found that estrogen caused the skin to become thinner. The other steroids they tested, progesterone, testosterone, and pregnenolone, acted in the opposite direction, making aged and atrophied skin thicker and more regular. They also made the pigment cells larger, and increased their branching.[1]

Since these hormones were already known to have protective actions against cortisone and estrogen, these results were not too surprising, though they did directly contradict the claims of people who made estrogen-containing cosmetics.

Since progesterone and pregnenolone do not cause healthy, young skin to thicken, their effect in damaged skin is probably partly to replace the deficiency of that type of steroid which occurs with aging, and to offset the damaging effects of the catabolic hormones, whose influence does not decrease with age.[2]

Many years ago it was found that in old age a woman's estrogens were increased relative to the 17-keto steroids adrenal androgens. Later, it was found that the conversion of androgen to estrogen increases with age in both men and women, and that this occurs largely in fat cells. Several years ago, P. K. Siiteri found that low thyroid modified the enzymes of fat cells in a way that would tend to increase the conversion of androgen to estrogen. More recently, it was found that adding progesterone to the enzymes had the opposite effect of aging and hypothyroidism, protecting the androgen from conversion to estrogen. These researchers (C. J. Newton and colleagues, of London) concluded that the decreased output of progesterone after the menopause might account for the increased production of estrogen.[3] Since progesterone declines in aging men, too, this could account for the same process in men.[2]

Vitamin A's effect on the skin opposes that of estrogen.[4] There are several mechanisms that could account for this. Vitamin A is used in the formation of steroids, and since the skin is a major site of steroid metabolism, vitamin A might help to maintain the level of the anti-catabolic steroids. A deficiency of vitamin A causes excessive release of the lysosomal enzymes, acid hydrolases, resulting in tissue catabolism.[5] Also, vitamin A is necessary for the proper differentiation of cells in skin and other membranes. A deficiency tends to cause an increased rate

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of cell division, with the production of abnormal cells, and a substitution of keratinized cells for other types. Estrogen also promotes keratinization and speeds cell division. A deficiency of vitamin A can cause leukoplakia in the mouth and on the cervix of the uterus; although this is considered "pre-cancerous," I have found it to be very easily reversible, as I have discussed elsewhere.[6] I suspect that the intracellular fiber, keratin, is produced when a cell can't afford to do anything more complex. Adequate vitamin A speeds protein synthesis,[7] and allows it to be used more efficiently.

Prolactin (which is promoted by estrogen, and inhibited by progesterone) increases with stress and with age. It probably affects every tissue, but it seems to have its greatest effects on the secretory membranes. It is known to have strong effects on the kidney, gut and skin (sweat and oil glands, hair follicles, and feathers in birds), and on the gills of fish. Its involvement with milk production suggests that it might mobilize calcium from bones, and in fact it does contribute to osteoporosis. This was foreseen by G. Bourne, in his book on the metabolism of hard tissues, when he suggested that estrogen, acting through the pituitary, might be expected to promote osteoporosis.

Since reading Bourne's book, I have doubted that it was rational to use estrogen to prevent osteoporosis, especially when it is known to be carcinogenic and when the ratio of estrogen to androgens and progesterone increases after menopause. Now that several publications have appeared clearly showing that estrogen increases prolactin, that prolactin increases with aging, and that prolactin contributes to osteoporosis, the postmenopausal use of estrogen is worse than dubious. But this was exactly when the pharmaceutical companies needed help in continuing to sell their profitable estrogens, and this was exactly the time when the FDA came out with its official approval of estrogen for preventing osteoporosis.[8]

Some doctors combine estrogen with testosterone, and this is much safer and more likely to keep the bones healthy. But since testosterone, like estrogen and cortisone, causes the thymus gland to atrophy, it is not a very good idea for chronic use, even if it doesn't cause masculinization. The other anti-estrogens, which are present at high levels in young women, include progesterone and DHEA. I have seen several publications which I think would justify the use of physiological amounts of DHEA to prevent or to treat osteoporosis,[9] and a few which support the use of progesterone.[10,11] My own observations on their use in osteoporosis have been presented many times at alternative medical conferences since the 1970s, but the main-line medical journals and conferences have declined to accept my reports, even when they advertise that all papers submitted will be presented in some form; many physicians believe that they are being presented with a fair sampling of the work being done in endocrinology, when in fact they are being given intensive advertising sessions.

Since it is known that cortisol causes bone loss, and it is widely accepted that progesterone has an "antiglucocorticoid" action, it is reasonable to think that progesterone should protect against bone loss, and that it is a progesterone deficiency after menopause which is a major factor in the development of osteoporosis. In the first edition of *Nutrition for Women* (1975) I pointed this out, in comparing menopause to Cushing's disease. Nencioni and Polvani more recently made observations which support this mechanism, in which progesterone "exerts a protective effect," by blocking the corticosteroid receptors. They observed "that the process of rapid bone resorption starts before the onset of amenorrhea and the abrupt fall in the estrogen levels and coincides with decline in progesterone secretion."[11]

By improving blood circulation and oxygenation of the tissues, progesterone and pregnenolone will decrease the need for the body to produce cortisol. Pregnenolone acts in the brain to decrease the basal secretion of ACTH. This protective effect is more basic than that achieved by blocking the cortisol receptors.

The early tests of the toxicity of vitamin A used cartilage in tissue culture. The same enzymes which are released by a deficiency of vitamin A are released by a large excess, causing dissolution of the cartilage. Other studies showed that a vitamin A deficiency caused similar changes in both bone and cartilage. Although much vitamin A is consumed in the production of progesterone, these studies show a direct effect of the vitamin on tissue stability. Although I believe that a vitamin A supplement will offer considerable protection against osteoporosis (and also against aging of the skin), it is important to remember that excessive vitamin A inhibits the thyroid, and that there is less risk of toxicity when vitamin E is supplemented too. I think many of the headaches currently associated with vitamin A use are the result of a preservative in the capsules (probably a sulfite), since some people who react to the vitamin in capsule form don't react when they use a specially ordered bulk form prepared without preservatives.

Things which damage skin and bones also damage other tissues, and things which protect them also protect other tissues. The protective factors include hormones (thyroid, DHEA, progesterone, and pregnenolone), vitamins A and E, and minerals – including magnesium, calcium, and sodium. Sodium spares magnesium, and helps to make albumin function in regulating blood and tissue water content. Under some conditions, sodium can act as an antioxidant. Since the unsaturated oils (and their prostaglandin derivatives) decrease respiration, cause stress to be more harmful, and have some specific effects that promote aging of skin, bones, and other tissues, the use of coconut oil is especially important. I think its use is one of the factors that prevents osteoporosis in tropical countries.

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Origins of Progesterone Therapy

Ray Peat's Newsletter

By the beginning of the 20th century, the idea of extracting regulatory substances from animal tissues was coming into general acceptance in Western medicine. J.A. Lebreton, in Paris, was one of the first to argue for the therapeutic use of an extract of the corpus luteum. Around 1904, C.F. Burnam, of Baltimore, began using corpus luteum of the sow, administered orally, to treat the nervous symptoms associated with menopause or with the menstrual cycle, and also to treat functional amenorrhea, obesity, sterility, and habitual miscarriage. (1912 edition of *New and Nonofficial Remedies*, and *JAMA*, August 31, 1919, 1ix, p. 698.) By the 1920s, tablets of desiccated corpus luteum were generally available, and the daily dosage recommended (representing 6 to 18 grams of fresh tissue) contained a very substantial quantity of progesterone.

The chemical structure of pure cyrstalline progesterone was determined in 1934 (by Butenandt), and within 2 years many publications were reporting the beneficial effects of injections of the purified material. By 1935, animal research was confirming that the therapeutic work previously done with the crude extract had been on the right track. Although the early research showed that progesterone was very beneficial in threatened miscarriage, arthritis, infertility, cancer and functional diseases of the nervous system, interest in this generic, public-domain material faded as the pharmaceutical industry found methods for converting it into proprietary synthetic glucocorticoids, estrogens, and progestins.

Animals are generally more sensitive to progesterone than humans are, and in animals no toxic level has been found, except that in the highest doses it is anesthetic. In humans, even this effect has never been reported in the medical literature, and it is clearly anti-toxic in nature. Besides preventing acute poisoning of many kinds, it also reduces the incidence of birth defects and cancer.

Progesterone, The Protective Substance of Youth

In 1971, I discovered that vitamin E and progesterone work together to sustain efficient production and use of biological energy.[1]

In the mid-1970s, I found that progesterone is the most powerful order-preserving substance (anti-chaotropic) on the cellular level, and that this explains its range of protective actions, from anti-toxic to anti-stress.[2,3]

Around 1980, I discovered that vitamin E, with its crucial effect on the mitochondrial respiratory enzymes, is a uniquely powerful, stable, and biologically compatible solvent for progesterone.[4]

Their intimate association at certain cellular sites requires mutual solubility. This property of mutual affinity extends to all biological areas, meaning that the solution of progesterone in vitamin E can be administered with exceptional efficiency by application to the skin or other membranes, or by ingestion, where normal digestive processes convert it into chylomicrons and distribute it to all tissues, allowing it to escape the tendency of the liver to convert it rapidly to an excretory form, as occurs when progesterone is administered in other forms.

Because of its profound biological compatibility, the progesterone-vitamin E solution permits otherwise impossibly high doses to be given, increasing by as much as 2,000% progesterone's already dramatic effects in a wide range of major biological problems, including epilepsy, habitual miscarriages, auto-immune diseases, and cancer of the uterus, breast, and kidney.

Some Aspects of Basic Progesterone Research

By 1945, Hans Selye had demonstrated that progesterone in itself has the full spectrum of regulatory and anti-stress functions of the adrenal steroids.

A little later, Albert Szent-Gyorgyi showed that progesterone is able to regulate the heart, in a manner similar to digitalis. In the 1970s, I demonstrated that it acts similarly on vascular smooth muscle, regulating its tone and preventing venous pooling of blood, and maintaining normal filling of the heart, opposing shock. The immediate improvement in circulation can have dramatic effects, which include restoration of kidney function, elimination of fluid from the lungs, restoration of sensation in the feet, and healing of gangrenous toes.

It restores normal tone to other smooth muscles, including the gall bladder, urinary bladder, intestine, sphicters, and uterus.

Progesterone's ability to regulate thresholds of cellular excitation operates in nerves, as well as in smooth and cardiac muscle. It sensitizes nerves that regulate respiration, and has been used to treat infant apnea, sleep apnea in adults, and polycythemia vera in men.

In cases of specific progesterone deficiency in men, small doses can cure impotence. It has been used effectively to treat benign prostatic enlargement.

It normalizes fluid pressure, as in bursitis and glaucoma treatment.

It restores many of the functions of aged skin, and is the normal defense against calcium loss from bones.

It is one of the few essential requirements, besides nutrients, for nerve (brain) cell growth and survival. In young people of both sexes, the brain contains more progesterone than other organs do.

It is reasonable that progesterone, the dominant hormone in pregnancy, should have a full range of protective functions to protect the vulnerable organism during its intra-uterine life.

Practical Issues

A typical dose of progesterone/vitamin E, 20 mg/day for 10 consecutive days, costs about $1.00 per month, at the present retail price.

Pharmacists have the authority to compound drugs as they choose, just as physicians can prescribe the formulation they prefer.

Neither progesterone nor vitamin E has any toxicity when used orally.

Under federal law, a prescription is needed for a dosage form of a drug that is potentially harmful. In practice, the very dangerous injectable insulin is always sold without need for a prescription, presumably because its use is conceived as akin to nutrition, providing an essential natural substance to restore a natural function of the body. By analogy with insulin, the infinitely less dangerous progesterone should not require a prescription.

The logcal way to make progesterone/vitamin E available to the public would be to license the patent to a chain of drugstores.

The availability of this effective and economical form of progesterone can hardly be kept secret, because people tell their friends, and patients eventually convince their physicians that it works.

An exclusive licensing agreement would be possible with 10% royalties, based on the retail price, with a guaranteed sales volume, and with lower royalties for larger volumes.

Economic Questions

Because of its absorption by a natural digestive route which distributes it to all of the tissues, progesterone dissolved in vitamin E is almost 100% absorbed when taken orally. Less than 1% is absorbed from some types of suppositories, and less than 5% absorption is typical. Taken orally as a micronized powder, pharmaceutical efficiency is only slightly better.

Most of the valid human research before 1981 used intramuscular injections of progesterone dissolved in vegetable oil and benzyl alcohol. Benzyl alcohol has a high affinity for water, and in contact with the tissue fluid, it leaves the mixture, causing progesterone crystals to form, since vegetable oil is a poor solvent for progesterone. Therapeutic blood levels of progesterone can be achieved by intramuscular injections, but at the cost of leaving toxic debris at the site of injection. Benzyl alcohol is a powerful neuro-toxin, but its harm is reduced by progesterone's anti-toxic action. The cost of the injectable progesterone, and of the injection itself, has been the main factor preventing wider acceptance of this form of progesterone in the United States.

Natural progesterone, and closely related steroids, occur in a wide variety of organisms. Up to the present, the cheapest source of the raw material has been the wild Dioscorea yam of tropical Mexico, but soybeans have also been used as the source of a steroid for production of progesterone. Since the soybean is a major source of vitamin E, the finished product can be made anywhere the bean is produced. Fenugreek, a quick-growing plant, contains the same substance as the Mexican yam, and can also be used as a source of vitamin E.

The chemistry for converting crude diosgenin into pregnenolone, and for converting pregnenolone into progesterone, is very simple, and can be done with little capital, at the site of production of the raw material. Interstate commerce needn't be involved, except for the economy of scale.

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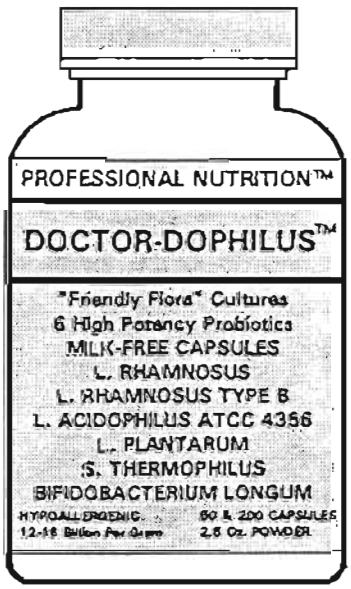

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Townsend Letter for Doctors & Patients, June 1996, Page 83 – 85

Q: You mention sunlight as beneficial to your health. How?

For example, it can cure depression, improve immunity, stimulate our metabolism while decreasing food craving, and increase our intelligence.

Although exposure to sun does contribute to aging of the skin, people who spend years working outdoors have a reduced incidence of cancer of internal organs. For many years, it has been known that the death rate increases during the winter months and also increases at night (winter or summer). Most deaths occur just before dawn when the body is in its least efficient state. It is just in the last few decades that we have been learning the reasons for this beneficial effect of light. It turns out that daylight stimulates our ability to use oxygen for energy production, and protects our tissues from some of the free-radical toxins that are produced by normal metabolism, by stress, or by radiation.

While ultraviolet light, and even blue light, tend to suppress our cells' ability to produce energy, those types of light penetrate only a short distance into living tissue, and so it is mainly the skin which is damaged by too much sunlight. Since blood does circulate in the layers of skin which receive ultraviolet rays, prolonged sun exposure can damage the immune system by injuring white blood cells, but usually the stimulating effect of the other types of light that penetrate more deeply offset this effect on the immune system.

Many health food stores are now selling melatonin, to reduce sleep and " prevent cancer. " They have taken some information out of context, and don't realize how dangerous melatonin is. It makes the brain sluggish, causes the sex organs to shrink, and damages immunity by shrinking the thymus gland. It is the hormone of darkness and winter, and is produced in the pineal gland by any stress which increases adrenalin. Adequate sun light suppresses the formation of melatonin.

This means that the immune system is most responsive in the summer, when days are long. Daylight stops the stress reaction, and protects our immune system.

Q: Doesn't exposure to the sun age you?

This effect is variable, and depends on our hormones and diet.

The unsaturated oils have been identified as a major factor in skin aging. For example, two groups of rabbits were fed diets containing either corn oil or coconut oil, and their backs were shaved, so sunlight could fall directly onto their skin. The animals that ate corn oil developed prematurely wrinkled skin, while the animals that ate coconut oil didn't show any harm from the sun exposure. In a study at the University of California, photographs of two groups of people were selected, pairing people of the same age, one who had eaten an unsaturated fat rich diet, the other who had eaten a diet low in unsaturated fats. A panel of judges was asked to sort them by their apparent ages, and the

subjects who consumed larger amounts of the unsaturated oils were consistently judged to be older than those who ate less, showing the same age-accelerating effects of the unsaturated oils that were demonstrated by the rabbit experiments.

While it is important to avoid overexposure to ultraviolet light, the skin damage that we identify with aging is largely a product of our diet.

Q: Don't you have to avoid sunlight because of skin cancer?

The type of skin cancer which is clearly caused by sunlight is a relatively harmless type of cancer, which appears only in sun-damaged skin. Melanoma, which is often called a skin cancer, because it sometimes begins in moles, does not have such a simple relationship to sunlight, and its incidence is significantly increased by the use of estrogen.

It is often said that the great increase in deaths from melanoma during the last 60 years has been caused by an increased popularity of sunbathing, but during the same time there has been a great increase in the incidence of cancer of the prostate, which is in a location that gets very little exposure to light. What these two cancers have in common is a sensitivity to estrogen, and it is during this same period of time that we have been exposed to increased amounts of estrogen-like chemicals in the environment as a result of industrial pollution: Dioxins, phenols, chlorinated hydrocarbons, DDT, smoke, etc. It is likely that these cancers (and others) are caused by the estrogenic pollutants.

The incidence of melanoma is consistently lower at greater elevations, where ultraviolet light is more intense, than at lower elevations. It is common for melanoma to develop on relatively shaded areas, including the middle of the back and the inside of the thigh, unlike the ordinary less malignant skin cancers, which develop most often on the forehead, nose, ear, cheek, and lip, where sun exposure is greatest. People who work outside have a low incidence of melanoma according to some studies, and this is sometimes said to be because they don't get sunburned, as pale people do when they spend time in the sun after being indoors for long periods. Sunburn does cause freckling, which is a clumping of pigment cells, but recent studies show that children who get sunburned are not at increased risk for melanoma. Sunburn causes complex changes in the tissue, including weakened immunity.

To avoid the aging and immuno- suppressive side effects of sunlight, it seems best for sunlight to come through a window glass which removes most of the ultraviolet light, and some of the blue light. Plastic film is available which contains copper that removes this harmful part of sunlight, and can be applied to ordinary window glass. Sitting in sunlight coming through a window of this sort, for short times during the day, is very protective. Besides protecting against cancer, it helps to keep the mood and energy level high, by keeping melatonin low and stimulating metabolism.

Recently, the polyunsaturated oils have been identified as the main thing in cells that radiation interacts with, to cause cellular damage. Vitamin E, taken internally or even applied to the skin, has been found to reduce the damage produced by exposure to

ultraviolet radiation, which is logical, since it interrupts the chain reactions of toxic free-radicals produced when unsaturated oils are oxidized by radiation or other injury. Aspirin has been found to have a similar effect in reducing the harmful effects which develop in the skin after sunlight overexposure. Coconut oil has been used for generations in " suntan lotions, " and whether it is absorbed through the skin or eaten as a food, it clearly has a protective antioxidant function. Carotene seems to work with vitamin E in the skin to reduce injury by ultraviolet radiation. Caffeine also has shown a protective action against radiation, but its mechanism of action isn't clearly understood.

Q: Why not use sun-blockers, so you can get light without getting burned?

If a sunscreen lotion is based on the use of an opaque reflective material, such as zinc oxide or titanium oxide, that substance remains mostly on the surface of the skin. This should make it fairly harmless, though it is possible that traces of titanium could be absorbed with oils into the skin, where it could be made toxic by interaction with ultraviolet rays.

However, other chemicals used in the sun screen lotions, such as PABA derivatives, also react dangerously with light, and are easily absorbed in significant quantities into the deeper layers of the skin, where they can cause mutations.

For example, several recent studies have found that the sun-blockers, which decrease the ordinary skin damage caused by ultraviolet rays, actually increase the risk of developing melanoma, by causing mutations when the cells' chromosomes interact with the sunscreen and the light. (Something similar happens in the disease, porphyria. A pigment that accumulates causes the skin to become very sensitive to the sun. Estrogen is known to intensify the disease.)

Even natural colored compounds, which have sometimes been used in suntan lotions, should be avoided, since they might be able to transmit the energy of light to the chromosomes, causing mutations.

Radiation from the sun reacts with the unsaturated fats you have eaten to cause oxidative damage to skin cells. Vitamin E, vitamin A and carotene are antioxidants that prevent skin cell damage, when they are taken internally or applied to the surface of the skin. None of these causes any harmful effects in the sun.

Aspirin reduces the iron content of the blood serum, and also inhibits the formation of the sometimes-toxic prostaglandins from fatty acids. Coconut oil is very resistant to radiation damage and, like vitamin E, tends to stop the chain reactions that occur in unsaturated fats. The old formula for suntan oil, coconut oil with iodine, might turn out to be a safe sunscreen, since the brown iodine absorbs light, as other " U.V. blockers " do, but iodine is also an effective chain breaker that inactivates free radicals, and it can't be absorbed into cells in its brown form. It doesn't have the potential for causing cancer that the popular sunscreens do.

Q: Is sunlight still beneficial if you use a safe sun blocker?

The popular chemical sun blockers are meant to stop the ultraviolet rays. If they can do that, without increasing the risk of melanoma, then they are very beneficial, because this will allow you to get a long exposure to direct sunlight, which penetrates deeply and has an anti-stress effect. But so far, there is no research that shows any of the chemical ultraviolet blockers is safe.

Q: Why do people seem to get sicker in the wintertime, often right after Christmas?

Nights are much longer in the winter, and even in the summer, death rates are higher during the night than in daytime. December 21 is the day with the fewest hours of sunlight, but the cumulative damage of prolonged darkness reaches its peak about a month later. Cold temperatures do have some harmful effects, but by keeping people indoors, or bundled up in thick clothing, cold weather also causes us to get very little exposure to sunlight. Winter sickness is mainly the result of a ” light deficiency. ”

When young sailors spent 6 months in the continuous polar night of Antarctica, they developed the same signs of nocturnal stress that are common in old people during the night. Many old people habitually get up before dawn, because they find it impossible to stay asleep. Even healthy young people (and animals) experience some degree of nocturnal stress as soon as the light is turned off at night, and their body responds with an increased production of adrenalin and cortisol.

The energy-producing part of cells, the mitochondrion, shows signs of being increasingly damaged as the night progresses, but they are gradually restored to their normal condition during the daytime light hours. This means that our greatest ability to resist stress is in the late afternoon, and we are most susceptible to injury at dawn. In the winter, nights are long and days are short, so we experience a cumulative increase in our susceptibility to stress-injury during the winter months.

The light which penetrates deeply into our tissues (mainly orange and red light) is able to improve the efficiency of energy production’ and to suppress the toxic free-radicals that are always being formed in cells.

Q: Can you get enough sunlight during the summer to hold you through the winter?

No, many of the beneficial effects of bright light disappear during just a few hours of darkness, though the restoration of our tissues that happens during the summer puts us into a better state for surviving the winter, for example by allowing massive regeneration of the thymus to occur. (This occurs in adults, not just in children. The idea that the thymus disappears after puberty is based on autopsies. If a person lives for even 3 hours after an accident or the onset of sickness, the thymus has had time to shrink.)

Frequent short exposures to bright light is almost as valuable as continuous sunlight, and it is less likely to cause skin aging.

Q: How much sunlight do we need a day for general health?

If artificial light is bright enough, it is as effective as sunlight at stopping the stress reaction, but people seldom use lights that are bright enough. Generally, people and animals are healthier when days are longer than 12 hours, that is, after March 21 and before September 20. When days are shorter than 12 hours, artificial lights should be used from sunset until bedtime, but the greatest brightness probably doesn't have to be continuous. Studies on isolated organs and tissues suggest that a few seconds of penetrating bright light are enough to break the free radical chain reactions, slowing the production of toxic substances, which tend to increase in concentration during nocturnal stress. A few seconds' exposure to the direct light of ten 150 Watt incandescent bulbs, for just a few minutes every two or three hours, might provide more effective protection than continuous exposure to a single 100 Watt light.

Glossary

Mutations are changes in DNA molecules which can kill cells, or accelerate their aging, or contribute to the development of cancer.

Cellular respiration: the ability of cells to consume oxygen and produce useful biological energy.

Free radicals are parts of molecules that can be produced by radiation (including sunlight), which contribute to cells' aging, cancer, and mutations.

The thymus gland is an essential part of our immune system, and it shrinks when we don't get enough light.

Melatonin, or pineal hormone: the pineal gland in the brain responds to an absence of light (or to any stress which increases the adrenalin systems) by secreting a hormone called melatonin, which lightens the skin, makes the brain sluggish, turns off thyroid and progesterone production, and suppresses immunity and fertility.

Immunosuppression refers to any process that lowers the efficiency of our immune system, such as stress, radiation, or poisoning.

Summary

1) In fall and winter, use very bright incandescent lights daily from sunset until bedtime.

2) Expose as much skin as possible to the bright light; even a minute is better than nothing. Thin, light-colored clothing transmits a considerable amount of light.

3) Infrared bulbs, with clear glass, are especially beneficial. Special low temperature red lights are available.

4) It is better to get your sunlight through windows, because it has less ultraviolet light than direct sunlight.

5) Don't use sun-blocking lotions, other than the simply reflective type (zinc oxide or titanium oxide).

6) Decrease the use of unsaturated oils in the diet, and use coconut oil as food and also on the skin during exposure to direct sunlight.

7) Vitamin E and aspirin reduce the harmful effects of sunburn, even when used after exposure to the sun, they can be applied topically to the burned skin. Vitamin E often contains some soy oil, so I recommend small doses of about 100 ma. per day.

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More Letters

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Response to "Sales Pitch for Linseed Oil"

Editor:

It is unfortunate that a Newsletter such as yours, with an editorial policy of openness to nutritional ideas and metabolic therapies, occasionally publishes material which is the result of incomplete information. It is still more regrettable, however, that the author of such an article then uses this 'information' to level ugly attacks on others.

Dr. Raymond Peat, in his article on "Sales Pitch for Linseed Oil" makes a number of statements which are not defensible. For instance, Johanna Budwig is a licensed and accredited M.D., which Peat does not mention. On the contrary, he puts her "scientific work" in quotes, implying that it may be pseudo-scientific. Dr. Budwig has documented results in reversing metastasized cancer with her use of flaxseed oil in combination with milk proteins (Quark: cottage cheese). Peat attacks her work with statements about linseed oil, quoting "It is known that..." Who knows? And do these unnamed persons heal cancer?

Udo Erasmus is thoroughly familiar with the chemistry of fats and oils and has worked for some time as an observer of Dr. Johanna Budwig's work. The expressed "suspicion" by the author that neither Erasmus nor Budwig have studied organic chemistry is another snide remark.

When authors make statements about effects of materials, it is always a little dangerous when these substances are "controversial." The supposed deleterious effects of unsaturated oils, discussed by some researchers, can be disproven by others.

However, when Peat quotes Dr. Gerson's work and refers to Gerson's book, *A Cancer Therapy*, of which he purchased the first edition published by Dr. Gerson while he was still alive (1958), Peat could not have read Appendix I of the second edition which discusses various items in respect to linseed (flaxseed) oil. Peat could not have known that:

1. During the last year of his practice, after the first edition of his book was published, Gerson added linseed oil to the diet of his cancer patients with excellent results. (*A Cancer Therapy* – 2nd ed., pp 397-398).

2. Dr. Gerson wrote an unpublished letter to Professor Albert Schweitzer, in 1958, which we later published in the Gerson Institute's Newsletter #3, Sept/Oct 1984, as follows:

"You will be interested to know that after years of effort, I have succeeded in stimulating the fat-metabolism without bringing malignant cells back to life. All previous efforts failed even after many months of improvement, as cancer cells flared up when oils were added to the diet. I found finally that linseed oil, when cold pressed and prepared without chemical additives, is extremely valuable.

In far advanced cancer patients, we give two tablespoonfuls of linseed oil daily for a short period of time; then one tablespoon, and later still less. Linseed oil has three unsaturated fatty acids. It is said to be the only oil in the world with these properties. According to the literature, especially in papers by Johanna Budwig from Munster (Westphalia, Germany) it seems that these fatty acids stimulate the reticular tissue, the reticuloendothelial system, and the various systems of the visceral nervous system. The above tissues comprise the defense and healing mechanisms of animal and human bodies, deeply united and accumulated in the liver. The conclusion has been drawn that no animal or human body is able to synthesize linseed oil molecules. Therefore, it must be given for a long time in minimal quantities."

Dr. Gerson, in the years of his practice, had experimented with various oils to try to obtain the desired effect which Budwig was obtaining, but had found that the oils he tried only caused tumor tissue to regrow. That explains the urgent admonition in his book, *No Fats – No Oils*. But when he found the linseed oil with its unusual properties, he obviously changed his mind. Since this discovery, as well as the contact with Budwig, postdates the publication of Gerson's first edition of *A Cancer Therapy*, clearly Peat did not find any reference to Budwig nor to linseed oil in that edition of the book.

It is unfortunately true that in today's world many "scientists" prostitute their work to industry and its demands – in other words, money. Peat assumes that Erasmus is guilty of this commercialism; another false assumption.

Readers interested in improving their health may want to acquaint themselves with Udo Erasmus' excellent book, *Fats and Oils*, and the Gerson Institute's Newsletter #22/23, "Fats that Heal – Fats that Kill," as well as Dr. Gerson's book, *A Cancer Therapy – Results of Fifty Cases*. All are available from the Gerson Institute.

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Unsaturated Oils Have Deleterious Effects

Editor:

I agree with your recent remarks about directing criticism mainly toward the errors of conventional medicine, because the biggest problems exist within the orthodox and government-established medical system. As you said, people should not be put down because of their degrees, and for that reason I avoid putting letters after names, except when there is a reason for it. However, I got a letter from Charlotte Gerson criticizing me for failing to mention Budwig's degree. Since the other degrees (including mine) were editorially added to my letter, it wasn't my intention to slight Budwig for being degree deficient.

However, Charlotte Gerson also says that I made "a number of statements which are not defensible," but doesn't seem to understand what I said. I am aware that linseed oil has been used by Mexican physicians to treat cancer at least since 1939, and that it can be toxic to cancer cells (though probably less toxic than to normal cells*), and that its laxative action is plausibly effective in treating constipated cancer patients. My primary criticism is that people who get on the big marketing bandwagon (whether the product is linseed oil or germanium or iron supplements) so often – as in the Udo Erasmus book – appear to systematically lead attention away from the possible dangers of their product.

The "deleterious effects of unsaturated oils" have been clearly established and are recognized by everyone working in the field. They are not "supposed" and are not merely "discussed" subject to disproof "by others." Many people are now investigating a variety of theories that attempt to explain the specific nature of the toxicity.

The opinions credited to Budwig by Erasmus suggest ignorance of organic chemistry and biochemistry. If someone takes Dr. Budwig's ideas seriously, *TLfD* should invite her to explain them herself.

Without knowing more about the publication details of the new version of the book, *Fifty Cases*, and the letter that

Max Gerson supposedly wrote to Schweitzer, I wouldn't want to analyze all of the ideas ascribed to him. The original book, which I believe was reprinted several times without changes, even after his death, was a coherent scientific document. Posthumous "new editions" always raise questions.

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*Cancer cells are rich in antioxidants which protect them against free radicals. J. Duchesne, *Ann. Biol. XVI* (5-6), 1977, discusses this and gives references.

More Than One "Best" Test for Parasites

Editor:

I would like to take this opportunity to inform your readers of two very important points regarding state-of-the-art parasite testing.

First, the Great Smokies Medical Laboratory now offers the most comprehensive Ova & Parasite testing. We are the only lab that employs Enzyme Immunoassay for specific organisms, in addition to Immunfluoresence assay. EIA testing is 96% sensitive and 100% specific for searched organisms. Our staining techniques include proprietary stains that have increased our yields dramatically. These state-of-the-art techniques are performed as part of our "Intensive Ova & Parasite" test (cost $70.00). Our results report includes detailed commentaries and pictures of any identified organisms.

Secondly, I have some comments concerning the method of sample collection. We are the only lab that offers a choice of either rectal mucosal swab or feces sample submittal. Our preliminary data indicates that given the advanced detection techniques now being used, there may be little difference between sample sources. There just isn't enough current data to support a claim for either method at present. Unfortunately, the clinical trial that another physician and lab reference in their support of rectal mucosal swab is actually seriously flawed and incomplete. The clinical trials did not include duplicate sample testing and the therapeutic agents used for treatment were not specific for just parasites (they were broad spectrum antimicrobial). In order to rectify the current information "gap," Great Smokies Medical Laboratory is conducting the first true research project to answer this question. We are having participating physicians submit concurrently, both a rectal swab and feces sample, from 1,000 patients. We will process the samples at the same time, providing comparative results for the submitting physician and for the study data base. Cost to the patient is as if just one sample were submitted. Any physicians that would like to participate, please give me a call (800-522-4762) so that we can provide you with the special collection kits.

The Great Smokies Medical Laboratory has always provided economical stool evaluations employing methods that are constantly updated and improved. We are proud to offer these improvements to our Ova & Parasite detection procedures.

Stephen Barrie, N.D.
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Genital Mutilation

Editor:

Rituals, no matter how outrageous, are not easily eradicated. The castrations of male slaves in the Ottoman Empire and elsewhere, for instance, were practiced for many years. Although there is no humane justification for the barbaric custom of female genital mutilations, the perpetrators can easily rationalize.

However, before we succumb to our moral indignation and proceed to castigate or to enlighten the "backward" societies, let us take a quick look at the ritualistic circumcision of American males. Granting that the female mutilations, as described, are far more drastic than our male surgery, there are considerably more circumcised American males than the total number of circumcised and infibulated females in Africa and the Middle East.

Of course, we can also rationalize our genital surgery. However, would not the editorial comment "these mutilations are done to healthy organs and are, therefore, NOT ethical medical practices – they are brutal sexual child abuse" apply equally to our ritual as it does to theirs? It's not a secret that as a prophylactic measure, the male circumcision in America has not prevented venereal disease. Yet, the ritual goes on; the procedure is covered by health (?) insurance.

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Justifiably concerned about the clitoridectomies and infibulations on non-consenting children in Africa and the Middle East, has Hosken asked how many of the American circumcised children had consented to their mutilation? How many American males voiced their informed consent to get their penis surgically trimmed? Under these circumstances should we not abolish our own ritual of routine circumcision at the same time that we wish to convince the Africans to give up their rituals? Would we not then be less hypocritical?

On behalf of the preservation of female clitoris and male preputium...

Victor Penzer, M.D., D.M.D.
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Editorial Comment by Reba Be

I was wondering who would pick up on the circumcision of virtually all hospital-born American males! A century ago the only circumcised people were Jewish; nowadays most men are.

As a bra-burning 60's feminist I embrace the right to intervene & confound perpetuators of such body-altering abuses (earlobe-piercing of girl infants is another). How could I, as a philologically, contemplative parent, permit these enactments of such cultish, archaic rituals upon non-consenting children?

I wrestled long with both rabbis and the all-male OB/Gynos to keep intact the son born to me and I won. One of their favorite ripostes on this subject has been: what do I know? I don't even have the equipment! Sometimes I ponder on what men think they are doing in the field of OB/gyno!

As I didn't "have the equipment" and Ben's father, himself wholesomely intact, would be *in absentia* during those vital years when our body-sense is keenly developing, I interrogated him for his lifetime experiences. He gave me simple, explicit information about cleansing, lubricating & flexing with particular emphasis upon those hazardous years when skin & sinew seem to grow at different paces (puberty). I passed it all on to our son.

"turn the coach into a pumpkin" or vice-versa. (Perhaps the "Emperor's New Clothes" would be a better analogy?) I ask the *TL/D* readership to not be fooled.

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Recycling Placentas

Editor:

I would like that you let your readers know that I've appreciated a lot your article and that it made me laugh a lot! I've no other comments....

Tell your readers that if they want some more information (on a scientific level), I will not publish it anymore in your journal, but I can send them if they write me personally.

With my best placental regards or foetal regards (as you prefer...)

Docteur Paul Musarella
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On Recycling Placentas, Thyroid Suppression and Carpal Tunnel

Editor:

I am glad to see your comment, "Recycling Placentas," in the June issue. More such dialogue between authors and editors could make the magazine more interesting. Last month, I decided to wait to see whether others would comment on Musarella's statements. Since your comments covered many of the points that needed to be made, I'd just like to add some of my other reactions.

Usually, the authors of foolish medical claims at least have the slight virtue of pushing common errors to an absurd extreme, helping to make thoughful people more conscious of a problem they hadn't been paying attention to. But there are suggestions in Musarella's article that threaten to besmirch good research. I don't know what "Pr." might stand for, but Filatov is grammatically masculine (Filatova would be a woman's name), and in Russian medicine, the phrase "the Russian scientist Filatov" would be assumed to refer to Vladimir Filatov, after whom at least one Filatov Institute has been named. Vladimir Filatov was a pioneer in reconstructive surgery and in corneal transplants from cadavers. He found that corneas transplanted from cadavers that had been kept in cold storage for some time exerted a healing influence on adjacent tissues. He saw similar effects in reconstructive surgery using "tube-flaps" of skin, and concluded that tissues subjected to stressful conditions formed substances which promoted healing and regeneration. (Succinic acid and other dicarboxylic acids were identified among the "biogenic tissue stimulators." Succinate stimulates respiration and steroid formation, and protects against peroxidative damage. Filatov's work is an important complement to that of Engelhardt and Szent-Györgyi and Polezhaev and Meerson.) Because abscesses often formed when vital tissue was implanted, Filatov tried sterilized tissue, and found that it was as effective in stimulating healing and regeneration. At this point he realized that tissue extracts would have the same effects, and he made and used extracts from a great variety of "stressed tissues," including leaves. He published results showing that sterile extracts could stimulate regeneration of the optic nerve, and of various other tissues. Many years after he died, people at the Filatov Institute found that *extracts* of placentas were extremely beneficial to old people.

If there is a New Filatov who rejects the conclusions of Vladimir Filatov, and uses vital placental tissue, in a caricature of the experiments at the Filatov Institute, Paul Musarella certainly owes us an explanation, because his phrase, "the Russian scientist Filatov" is misleading. But I think Musarella is more likely just

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another person exploiting the gullible public, who are justifiably impatient with the failure of the medical establishment to work seriously on problems of aging and regeneration.

Although the *TL/D* deliberately avoids filtering out crazy ideas, I think a tiny editorial note at the end of such articles would be appropriate, commenting for example that no references were submitted, that the identity of "Pr. Filatov" wasn't explained, and possibly giving a little more information about the author.

Thyroid Suppression

In the June "Letters" section, there is an interesting discussion between Mona Morstein and J. Collin, with both assuming that there hasn't been clear research on the issue of thyroid suppression. It is easy for an excess of exogenous thyroid hormone to suppress the gland until there is no detectable endogenous thyroid hormone formed (using radioactive tracers), but the important point is that in normal people a totally suppressed thyroid function takes only two or three days to return to normal when the suppressive treatment is stopped. In a small percentage of hypothyroid people, treatment for a short time with thyroid supplementation can stimulate recovery of normal thyroid function, by activating the brain-pituitary system, raising blood sugar which activates the liver enzyme system that produces T3, and by lowering the anti-thyroid stress hormones. Without using radioactive material, it is easy to visualize the process of suppression: very obvious depressions in the neck thyroid region appear on a thoroughly suppressive dose, and reducing the dose for a few days restores the neck contour. This very rapid adaptation of the gland's anatomy and function to exogenous thyroid is necessary, because of the irregularity of our consumption of thyroid substance in a natural diet. Until this century, everyone ate the thyroid in various small animals, and we still get some in milk and shellfish and a few exotic foods.

The issue is different with thyroxin, T4. The bulk of our active T3 hormone is produced in the liver, as part of a quickly adaptive system for adjusting the metabolic rate in relation to nutritional status, but the pituitary is also able to convert T4 to T3, and a high level of T4 will cause suppression of TSH secretion, even if the liver is failing to produce the active T3, as

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in aging, stress, cirrhosis, and various other diseases. Thyroxin can literally make hypothyroidism worse. In this case you have suppression without a compensating absorption of active hormone.

Although a little thyroid substance is a normal dietary factor, and digestion of the glandular colloid converts the protein into the hormones in the same kind of process that occurs in normal secretion from the living gland, I agree with Morstein that it is important to restore the gland's normal function as far as that is possible. I think many of her suggestions derive from the endocrinology course I taught at NCNM in the 1970's, but I think some of the details are wrong. Normalizing the thyroid is now a pretty well defined physiological process, and the biggest problem is ideological, rather than technical. Many cultural forces, especially the drug companies, have made it hard for people to discuss thyroid endocrinology.

Carpal Tunnel Syndrome - Or, "The Sick Hand Scam?"

When a physician chooses the most profitable diagnostic and therapeutic approaches to a health problem, it is likely to be considered fraudulent if the doctor is a chiropractor, but not if the doctor is a surgeon. If a naturopath tells you that bed rest is the best treatment for a ruptured spinal disc, surgeons will warn you about the dangers of quackery, but the research clearly shows that, for safety and efficacy, surgery is distinctly inferior to bed rest. There are many other cases in which doing nothing, or using a more conservative treatment, is clearly superior to the standard medical or surgical treatment, but the medical industry has learned how to control public opinion by manipulating the mass media.

By consulting with thousands of women who believed they had a hormone imbalance of some sort that their physicians couldn't identify, I began to see several clusters of symptoms that responded immediately to a rational nutritional and hormonal anti-stress program. One of these clusters might be called Subtle Constellation of Absorbed-Mucoprotein-related signs and symptoms, or possibly sub-clinical myxedema, though neither term is likely to be widely adopted in the medical community.

Women are several times more likely than men to have "thyroid disease," simply because estrogen tends to block thyroid function. Estrogen-induced thyroid hypofunction can be compensated to some degree by various hormonal adjustments; elevated secretion of adrenalin and cortisol are common. When the compensation is inadequate, there will often be hypoglycemia and a tendency to form too much histamine. Too much adrenalin will cause cold hands and feet, too little will cause orthostatic hypotension (blacking out when you stand up too quickly) and bowel spasms, for example.

Various water-binding glycoproteins are formed under the influence of hormones or stress, but whatever proteins are in the blood, including albumin, will show up outside the blood vessels, around the tissue cells, when the blood vessels become leaky. Low thyroid, high estrogen, and high histamine are known to increase the permeability of blood vessels.

Patients who have myxedema typically have mitral valve prolapse, and at autopsy it can be seen that the valve is thickened into a jelly-like mass. Many women with the premenstrual syndrome have a mitral valve heart murmur premenstrually, but not at other times of the month. The jelly can be formed and removed fairly quickly.

Old textbooks on the thyroid gland often listed emphysema as a symptom of myxedema. When rats are given a large injection of estrogen, the oxygenation of blood in their lungs is sharply decreased in less than an hour. Although it is not common to test oxygen diffusion in humans, I know of two women in the same family who showed very poor pulmonary oxygen diffusion after they were put on high doses of estrogen. (Since estrogen inhibits thyroid secretion, and hypothyroidism is associated with elevated estrogen, they should be considered together.) Leakage of proteins from capillaries in the lungs is probably responsible for the decreased diffusion, by thickening the layer through which the oxygen must diffuse.

When myxedema exists in childhood, the cartilage in joints swells, and is deformed, causing a characteristic knock-kneed appearance. In milder form, the swelling can cause joint pain that doesn't involve the characteristic inflammation of arthritis. In a mild form, the calf muscles tend to swell after prolonged activity; the "growing pains" that are so common around the beginning of puberty are probably the result of a temporary hypothyroid edema of the leg muscles.

When a tendon swells, it is sometimes the result of a local injury or of a particular over-use of a muscle, and in these cases local treatment can sometimes produce a permanent cure. But when the problem keeps recurring, or keeps showing up in different areas, there is probably a general hormonal problem.

When a tendon in the wrist swells, it can cause numbness in the hand, by pressing on a nerve which passes through the carpal tunnel with some tendons. The tunnel is formed by a ligament that holds the tendons in place, and swelling of the ligament itself can contribute to compression of the nerve. Even the connective tissue that forms the nerve sheath itself can swell. Many people with undiagnosed hypothyroidism complain that they "have poor circulation," and that their hands and feet go to sleep easily. I think these are two separate (but related) problems. Low thyroid people often have cold hands and feet, and they often have nerves that are over-sensitive to compression. Poor oxygenation is involved in edema, both as cause and consequence but swelling can cause compression and nerve injury in a way that is exacerbated by certain postures or repetitive actions, and this compression can be relieved by surgery. But if the tissue was susceptible to swelling because of the general hormonal environment, other problems will follow. Pinched nerves and arthritis commonly follow treatment of the carpal tunnel syndrome by surgery or local cortisone injections.

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Only Very Good Testers Should be Selected for Tests, *Not Just Anyone*

Editor:

Thank you for your letter of April 16th 1990, regarding the VEGAtest-Method. It would be helpful for everybody concerned if you publish the following in the *Townsend Letter for Doctors:*

The VEGAtest-Method[1] was developed from the Electro-Acupuncture according to Voll.[2] Instead of measuring the skin resistance on organ-related acupuncture points e.g. liver, kidneys etc., in the VEGAtest-Method organampoules of liver, kidneys etc. in potencies of D4 and lower are placed in the measurement circuit and measurements are made on one suitable point only - connective tissue.[3]

Oral Absorption of Progesterone ♀

by Ray Peat, Ph.D.

Since many synthetic progestins are known to be luteolytic,[1] while progesterone itself exerts a positive feedback influence on steroidogenic tissue,[2] it is clear that it would be useful to have an effective way to administer progesterone orally.

It is well known that fat soluble substances are absorbed primarily by way of the lymphatic system, entering the general circulation directly rather than passing first through the liver.[3] Progesterone is extremely insoluble in water, but it is soluble in lipids. If the solution is stable, it seems clear that the progesterone will be preferentially absorbed by the lymphatic route.

I have investigated the oral use of progesterone in tocopherol, a non-toxic stable solvent, in cycling women with a luteal phase deficiency, and in post-menopausal women.

In younger women who are still producing large amounts of estrogen, a therapeutically effective oral dose of 50 mg. to 200 mg. daily (during the luteal phase of their cycle), was found to prevent the symptoms associated with the premenstrual decrease in serum progesterone which had been observed in previous cycles. In some women the effective dose caused the blood levels to rise somewhat above the levels usually considered normal for the luteal phase.

Post-menopausal women, who have much lower average levels of estrogen and who produce little progesterone, show much more clearly the effects of administered progesterone. Seven women who had gone through "natural" menopause at least two years previously and whose serum progesterone was either below the sensitivity limit of the competitive protein binding technique, or in the typically low post-menopausal range of measurement by radio-immunoassay, were given oral doses of 50 mg. or 100 mg. of progesterone in tocopherol.

The earliest any blood was drawn, after an oral dose of progesterone, was 20 minutes; in this case, the progesterone had risen from 0.2 ng/ml before, to 0.7 ng/ml with a dose of 100 mg. When blood was drawn from 4 to 8 hours after an oral dose of 50 mg. to 100 mg., the blood levels were between 6 and 16 ng/ml. No attempt was made to assure that the progesterone was taken on an empty stomach, and meals were eaten as usual while waiting for blood to be drawn. The progesterone was administered by their regular physicians, and the measurement was done by commercial medical laboratories.

In two cases in which blood was drawn 24 hours after a single dose of 100 mg., the progesterone level was still in the normal luteal phase range.

Since the observations were made over a period of several years, with progesterone measurements made at several different laboratories and by different techniques, the numbers aren't strictly comparable. We recently got a clearer picture of the rate of absorption in a fasting person. A middle-aged man, with a fasting level of 0.2, took 100 mg. At the first hour, the level was already 7.0 ng/ml; the concentration rose each hour to a peak at the sixth hour of 14.0 ng/ml, and the last observation, at the seventh hour, was 7.0 ng/ml. On average, men's livers are quicker to remove substances from the blood, and the fact that no food was taken during the test very likely caused the rate of increase and the rate of decrease to be greater than in a non-fasting person.

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Zinc and Alzheimer's Disease

Editor:

I read with great interest the editorial by Dr. Collin in the December *Townsend Letter* that zinc supplementation has a connection to amyloid clumping found in Alzheimer's disease. I have had Alzheimer's for over 12 years and have taken 50 mg of zinc, other vitamins, minerals, trace minerals, digestive enzymes and HCl at meals every day for over six years. A blood test from Princeton BioCenter indicated zinc and B-6 deficiency. Prior to taking zinc there were, for as long as I can remember, white spots on my fingernails.

I am not a medical specialist, nor am I trying to imply that Massachusetts General Hospital's research is inaccurate, but until there is more information than is presently available, I am reluctant to discontinue zinc supplementation.

Tom Warren
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Oral Progesterone is Not Inactivated by Stomach Acids, Pancreatic Enzymes or Liver Detoxification

Editor:

Stephen Dentali, commenting on my remarks about oral progesterone, has indicated that "any pharmaceutical text" can be consulted to understand certain issues in pharmacology and pharmaceutics.

Textbooks are useful for introducing students to a new subject, and they are an interesting literary genre, allowing us to see how the individual author handles a certain area of knowledge. But anyone who has seriously studied a subject knows that textbooks aren't intended to resolve scientific questions. Different authors sometimes take different positions on the issues. By reading many texts on a given subject, we can see that the people who write textbooks are usually far behind the decisive scientific work in most of the areas covered by their book. If they are researchers themselves, their particular area will usually be described in an up-to-date, though personally filtered, manner. Increasingly, publishers are influencing the content of textbooks, for the purpose of maximizing sales. (Richard Feynman's entertaining discussion of textbooks should be read by every teacher.) It is important to critically examine original scientific publications, but textbooks are generally so far removed from the original work that it would be a waste of time to criticize their subjectivity and inaccuracy page by page. That isn't necessary, as long as people realize that they shouldn't be treated as anything but secondary (or tertiary) sources.

More Letters

BIO-METABOLIC NUTRITION™

Important Notice

In the October 1994 issue of the Townsend Letter, Bio-Metabolic Nutrition™ inserted a brochure which made an incorrect claim. A diagram illustrated the complexity of natural vitamins and minerals and stated they are bonded to proteins, carbohydrates, lipids and bioflavonoids. The statement also claimed that GrowForm™ vitamins are bonded.

This is an incorrect statement and should not have been made.

There have been no tests performed which confirm this claim for GrowForm™ vitamins and minerals.

We sincerely apologize for this inadvertent error.

Sincerely,

Carl E. Jackson

Carl E. Jackson
President

More Letters

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Many textbooks have said that since insulin is a protein, and since proteins are digested in the stomach, insulin is inactive when taken orally. Since oral insulin can cause lethal hypoglycemia in dogs (whose capacity to digest protein is very great), we can see the limitation of reasoning without evidence. Progesterone happens to be very resistant to acid as well as to stomach enzymes, but ultimately the body is able to modify it into other substances, which are excreted.

Dentali invokes the "first pass" dogma of liver inactivation, but he neglects the whole point of what I said, namely, that chylomicrons are *not* consumed on the first pass though the liver. Progesterone equilibrates from the chylomicrons into the other fractions of the blood, and a large part of it is carried in the red blood cells. Laboratories which measure the progesterone (or pregnenolone, or DHEA) contained in the serum after removing the chylomicrons and red blood cells are probably following some old textbook dogma, without realizing that they have discarded a major part of the hormone they would like to measure.

Dentali seems to have been offended by my reference to the "bizarre crystallization" that occurs in some progesterone products, and by my reference to FDA errors. I will respond to those points.

If the products that are unstable oily solutions bore labels warning users to heat and stir the mixture before use, they might be acceptable. But some of the products are in opaque bottles, and the physicians who prescribe them are not likely to suspect that the progesterone crystals have settled to the bottom. My patent is based on the fact that vitamin E stably holds progesterone in solution, so that it can be assimilated effectively by any route, transdermally, vaginally, or orally. Various companies have tried to take advantage of the awareness that my formula works, but I think some people have assumed that any product which contains "vitamin E" and progesterone will work in the way I have described. In the case of opaque transdermal (or rectal or vaginal) creams, the progesterone crystals in bad formulations are harder to see. Spreading the cream in a thin film, they can be seen under a microscope. What is visible is not going to be able to go though the skin.

FDA officials have said that the only "approved" form of progesterone is the oily injectable form, which is described as progesterone dissolved in vegetable oil, with benzyl alcohol added as a bacteriostat. In "bacteriostatic water," benzyl alcohol may be present at 0.9% to 1.9%, and even at that concentration it is a dangerous neurotoxin and allergen. But the vegetable oil used as vehicle is a very poor solvent for progesterone; and it is not a hospitable environment for bacterial growth. (For example, it is a strong mutagen.) The so-called progesterone in vegetable oil needs the very high concentration of approximately 10% benzyl alcohol to stay in solution on the shelf. When such a solution is injected, the toxic alcohol diffuses away into the body fluids, leaving the (cancer promoting) vegetable oil with progesterone, and the progesterone crystallizes out of solution. The benzyl alcohol is the actual solvent that permits the progesterone to stay in solution while the product is on the shelf. The massive amount of this neurotoxin in the "approved" form of progesterone is reminiscent of the FDA's approval of a bronchodilator for asthma patients which contained metabisulfite as a preservative. When I told them that I thought that was an irrational product, since metabisulfite can kill people with asthma, and that the deadly "paradoxical" bronchoconstriction that was killing patients didn't seem paradoxical at all, they just didn't respond in any visible way. They similarly have not responded to the many complaints I have made about their "approved" form of progesterone. In another case, when I sent them evidence of what I believe is a gigantic and continuing drug fraud, they actually wrote me a letter saying they don't handle individual's complaints.

The FDA has done tremendous damage to women's health by claiming that natural progesterone has the terrible side effects of the synthetic progestins. This has never been a scientific issue: It is strictly a matter of the FDA's giving demonstrably false information to the public. Some of the widely used synthetic progestins have been powerfully estrogenic and teratogenic, while natural progesterone is neither.

Natural progesterone is known to be a safe and effective treatment for epilepsy, while *all* the recognized anti-seizure drugs are teratogenic, and it is largely the FDA's false attribution to progesterone of the side-effects of synthetic progestins that is responsible for the continued failure to make progesterone available to pregnant women with epilepsy.

Progesterone can be used as an anesthetic, but it is not correct to ascribe to it the properties of ether.

Progesterone has anti-inflammatory properties, but it is not correct to say that it must therefore have the properties of cortisol.

Progesterone has mineral-regulating properties, but it is wrong to classify it as a mineralocorticoid.

Long ago, Hans Selye pointed out some of the problems involved in classifying multiple action substances by one of their actions. But what the FDA has done goes far beyond any problem with sloppy scientific terminology. It has falsely claimed that the toxic properties of various synthetic drugs belong to natural progesterone. By their reasoning, if testosterone has a "progestational" effect on the uterus (as it does), then progesterone will produce whiskers and big muscles. If no one had tried to point out to them the egregiousness of their errors, I could believe that the FDA was innocently incompetent, but in fact they actively work to obscure the truth.

In this case, and in others that I have discussed elsewhere, I believe the FDA has taken irrational and antiscientific positions to protect the interests of the giant drug companies, to the great detriment of public health. They, and the companies they serve, should be held accountable for the death and disability resulting from their actions. Legally, I think patients, physicians, and pharmacists all have many bases on which to act against the abuse of power by people in the FDA. Illogical and arbitrary application of the law is simply illegal.

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PS: In previously published articles I have given references to the various points I make here.

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The Bean Syndrome

The Bean Syndrome

An extract of the common bean (phytohaemagglutinin, PHA) is widely used in research, and has been used occasionally in medicine. The effects of bean toxin, and other plant toxins (e.g., pokeberry) overlap in several ways with viral infection and autoimmune disease. PHA causes, for example, the appearance of large mononuclear cells in the blood, the suppression of DNA synthesis in thymic cells, a slight leucopenia, and hepatic necrosis. Extracts of lentils, broad beans, and fenugreek (used in curry) are as active as PHA, and extracts of common peas, chick peas, lupinus, and soy beans also have some activity. The effects of a single exposure (such as eating a pokeberry) can remain microscopically visible for two weeks.(1)

In aging, stress, and malnutrition, the barrier function of the intestine is weakened. Vitamin A and magnesium deficiencies allow macromolecules to enter the blood from the intestine.(2)

Injury to the bowel causes "flu-like" symptoms. There have been reports that the viruses of "respiratory diseases" appear in the intestine before they appear in the respiratory tract. Alvarez found that "when a dog gets distemper the gradient of latent period down its small bowel is reversed," and he suggests that in a cold "a systolic, non-progressive type of contraction appears." He says codeine is the best medicine to block a cold. (I have argued that it is vitamin C's laxative action which can interrupt cold symptoms.) Recent research shows that naloxone, the morphine antagonist, can restore normal responses to the stressed bowel. Alvarez was interested in chronic fatigue and "painful fatigue," and remarked that occasionally "a fatigue state will follow a bout with some infection such as influenza."(3)

Bacterial toxins, whether produced in the intestine or in the manufacture of food supplements, pass through the wall of the intestine in larger amounts in stress, malnutrition, and old age. Endotoxin suppresses mitochondrial respiration, and tends to produce a shock-physiology similar to that produced by endogenous hormones. I have mentioned before that I think endotoxin can be involved in the premenstrual syndrome, and I think it might even be involved in some breast syndromes.(4)

Two features of mitochondrial damage in severe stress (regardless of whether endotoxin is involved) are a depletion of the antioxidant reserves, and loss of the ability to convert cholesterol into the protective steroid hormones. Mitochondrial damage is more likely in hypothyroidism, as I have discussed previously; thyroxin inhibits lipid peroxidation, end it tends to be inversely related to adrenalin, preventing or minimizing "catecholamine toxicity," for example.

Beans and lentils happen to be powerful anti-thyroid agents, so it isn't surprising to see indications of decreased aerobic capacity, resulting from decreased peak oxygen consumption(5) in association with the chronic fatigue syndrome (CFS), if that syndrome is caused by chronic exposure to dietary legumes.

Hypothyroidism causes poor magnesium retention, so the report that a magnesium supplement caused reduced pain and improved energy level and emotional state, while increasing intracellular magnesium in CFS patients,(6) suggests a role for hypothyroidism in CFS.

One of the symptoms specific to chronic fatigue syndrome(7) - postexertional malaise, marked by pain and weakness and by an exacerbation of other symptoms including fever and adenopathy - can be explained as the result of increased absorption of bowel toxins which follows the relative ischemia of the intestine during intense adrenergic stimulation.

A day or more after eating an allergen, it can be resting harmlessly in the intestine, and exertion, or emotion, or hunger, or nighttime can lower the blood sugar enough to cause a surge of adrenalin. The adrenalin reduces the flow of blood to the intestine, allowing allergens to be absorbed via the de-energized tissues. If the blood sugar stays low in spite of the adrenalin, white cells will be stimulated to release histamine and other pro-inflammatory substances, but the adrenalin will also cause the secretion of glucocorticoids. Night-sweats and neurological symptoms can be produced by these hormonal responses. The glucocorticoids first induce, then - at high levels - destroy the detoxifying enzymes.

Special conditions, such as a bowel infection, or immaturity of the intestine, can allow large amounts of allergens to pass through the intestinal barriers. In Los Angeles, I learned that physicians and nutritionists often advise welfare mothers to start feeding beans to their babies at six months. In parts of Africa, babies are given "bean milk" from the beginning instead of milk.

The Epstein-Barr virus, which is believed(*) to cause Burkitt's lymphoma and infectious mononucleosis, has often been proposed as a cause of the chronic fatigue syndrome. R.J.V. Pulvertaft(8) found "a close similarity between Burkitt cells and human lymphocytes stimulated by bean extract." He concluded that "...the possibility of a relation between Burkitt's lymphoma and a diet of beans should not be neglected," though he emphasized that other factors must be considered, since most people who eat beans don't develop the disease. The intestinal parasites which are common in tropical Africa can cause inflammation of the bowel, leading to the absorption of large amounts of antigens.

Since the bowel becomes inflamed in influenza, it is reasonable to think that some of the symptoms of "the flu" are produced by absorbed bowel toxins.

The variations in the post-influenza syndromes are very likely influenced by the nature of the bacteria or foods which are present, chronically or at the time of an uncompensated stress or inflammatory disease. K.M. Stevens(9) has argued that while rheumatic fever and glomerulonephritis are caused by the antigens of streptocci, systemic lupus erythematosis (SLE) is probably caused by the antigens of grampositive lactobacilli found in the normal flora.

Migraine, SLE, CFS, thyroid problems, and some kinds of porphyria seem to be more common in women of reproductive age, and are often exacerbated by premenstrual hormone changes. According to Stevens, "SLE is almost entirely a disease of women of child-bearing age. One possibility for this selection could be that women during this period harbour a peculiar flora. This is indeed the case; large numbers of gram-positive lactobacilli are present in the vagina only during the thirty-odd years when regular menstrual activity is present." In 1974, I noticed that I consistently got a migraine headache after drinking a lactobacillus milk product, and stopped using (and recommending) yogurt and other lactobacillus foods, though I suspected it was the lactic acid which caused the symptoms. I still consider lactic acid to be a metabolic burden, especially when combined with an estrogen excess, but Stevens' main point, about the significance of our immunological response to systemic bacterial antigens, deserves more attention.

I have previously discussed the use of antibiotics (and/or carrot fiber and/or charcoal) to relieve the premenstrual syndrome, and have mentioned the study in which the lifespan was extended by occasionally adding charcoal to the diet. Recently, I heard about a Mexican farmer who collected his neighbors' runt pigs, and got them to grow normally by adding charcoal to their diet. This probably achieves the same thing as adding antibiotics to their food, which is practiced by pig farmers in the U.S. to promote growth and efficient use of food. Charcoal, besides binding and removing toxins, is also a powerful catalyst for the oxidative destruction of many toxic chemicals. In a sense, it anticipates the action of the protective enzymes of the intestinal wall and the liver.

Our normal defenses against environmental toxins include a surface layer of mucus, the IgA antibodies on membranes, the brush border of intestinal cells, on which protein digestion normally takes place, enzymes in the intestine and liver which hydoxylate and glucuronidate smaller molecules of toxins, and binding-proteins, such as albumin and metallothionein, all of which keep toxins from entering other parts of the body. When toxins get past those barriers, survival depends on other adaptive factors, including the catatoxic steroids and the antioxidative systems.(10, 11) Besides metabolizing exogenous toxins, the detoxifying enzymes of the monooxygenase system metabolize endogenous substances, including steroids, prostaglandins, and polyunsaturated fatty acids, which affect allergic reactivity. An imbalance of this system can waste the protective steroids.(12)

Recently, it has been argued that the allergic reaction itself functions as an immunological defense against toxins.(13) However, when the intestine and liver are injured, the production of cholesterol is often decreased to such a great degree that there isn't enough to maintain adequate production of the catatoxic and anti-inflammatory steroids. Many people with the allergic fatigue syndrome have a dangerously Iow blood cholesterol level of 90 to 130 mg%. (Fruit, because of its fructose content, usually helps restore liver cholesterol synthesis.)

Undercooked and raw plant materials in general are important sources of toxins and allergens. Legumes have recently become more important factors in the U.S. diet, because of a complex shift of ideology about the "healthful" diet, which is often associated with a compulsion to "exercise," and sometimes to use stylish, but toxic, food supplements such as tryptophan, iron, and manganese. Ascorbic acid tablets may be contaminated with enough iron and/or other

catalysts to produce a toxic amount of free hydroxyl radicals.(14) In a vegetarian diet containing very little vitamin A as retinol, carotene can sometimes become toxic, since its conversion to retinol requires vitamin B12 and other liver functions that seem to depend on adequate thyroid function, and excessive carotene can be anti-thyroid as well as anti-steroidogenic. A deficiency of retinol can damage the barrier functions or membranes, various immune functions including antibody formation, and the synthesis of protective steroids.

Some women with premenstrual fatigue have found that the "premenstrual" phase tends to get longer and longer, until they have chronic fatigue. I found that to be one of the easiest "PMS" problems to correct. When people are older, and have been sick longer, the fatigue problem is likely to involve more systems of the body. The larger the quantity of "toxic fat" stored in the body, the more careful the person must be about increasing metabolic and physical activity. Using more vitamin E, short-chain saturated fats, and other anti-lipid-peroxidation agents is important.

Sixty years ago, people with chronic fatigue were often said to suffer from "nervous breakdown," and advised to go to a sanitarium for a vacation, and to stop bothering the doctor. A change of activity, of place, of work, or of associates can sometimes be very therapeutic. Changing the diet can have social and ideological overtones, and can be done more easily while on a vacation trip. But sometimes the problem can be solved simply by avoiding some vegetable materials and food supplements, and/or by correcting hormonal problems, and/or by modifying the intestinal ecology.

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Note - (*) Antibodies to this virus can be found In 90% of the population, so it isn't very meaningful to say that it "causes" those particular conditions.

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By Raymond Peat
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Thyroid: Misconceptions

by Ray Peat, Ph.D.
Ray Peat's Newsletter

When I describe some of the simple ways the thyroid gland works, I know that I'm not answering the questions most people have. In the last 50 years, a culture, a mythology, related to thyroid hormone has been manufactured in this country. Now and then, people send me *JAMA's* latest contribution to that culture. The articles and advertisements in medical journals, and the more direct contacts between drug companies and physicians, have covered most aspects of thyroid physiology with a thick layer of misinformation. A very different story is found in journals of endocrinology, biochemistry, nutrition and metabolism, and in foreign books and journals.

Most of the misinformation is based on something true. If a similar preoccupation with possible harmful side-effects surrounded the rest of medicine as it does thyroid supplementation, medicine would disappear; if it surrounded dietetics, people would starve.

It is sometimes true that "if you take thyroid it will suppress your own gland." By overdosing people until the output of their own glands had gone to zero, it was possible to see what happened when the overdose stopped. Everyone's gland was functioning perfectly again within two or three days. Occasionally, a person whose pituitary isn't producing TSH will respond to thyroid supplementation with normalization of TSH and restoration of their own thyroid gland's function.

It is sometimes (but rarely) true that a person will seem healthy when his serum thyroxine level is near one of the extremes of the "normal" range (which is often given as between 4 or 4.5 micrograms per 100 ml. and 12 or 14 mcg. per 100 ml). The story behind that extreme range (imagine a similar "normal" variation for cholesterol, or sodium, or potassium, or anything biochemically important) has to do with a revision in the 1940s of the definition of "normal" to include 95% of the population, based on the PBI measurement, which was later found to be irrelevant to thyroid functioning.

Thyroxine is often called "the thyroid hormone," in the same way that estrogen has been called "the female hormone." Progesterone is quantitatively and functionally the most important female hormone, and triiodothyronine, or liothyronine, is functionally the most important thyroid hormone. It is the metabolically active derivative of thyroxine, somewhat as insulin is the activated form of proinsulin. When thyroxine is added to brain tissue in vitro, it suppresses respiration; but when triiodothyronine is added to any tissue, respiration is increased. Triiodothyronine (T3) is mostly produced in the liver, depending on the availability of glucose to the liver, allowing a sensitive adjustment of metabolism to nutrition.

Armour thyroid, USP, is often said to be of imprecise dosage, but in fact every batch is biologically standardized, and studies have shown it to be reliably within 1% of the labeled potency. The best known brand of the supposedly chemically precise levothyroxine, however, was for a long time 30% below the labeled potency.

If the liver is the main source of the thyroid problem, then thyroxine pills can make the problem worse, by suppressing the portion of T3 still coming from the thyroid gland. Armour thyroid, USP, Thyrolar, Euthroid, Proloid, and a few other products contain both thyroxine and T3, in approximately the proportion secreted by a normally functioning gland.

Unsaturated oils interfere with thyroid function in several ways, including blocking the "digestive" proteolytic enzymes involved in the release of hormone from the globulin. Unsaturated fatty acids interfere with binding of the hormone to a transport protein, and with the conversion of T4 to T3 in the liver and in the pituitary. Linoleic and linolenic acids are roughly twice as toxic to these systems as oleic acid is. The tissue response to the hormone is inhibited by unsaturated fats in proportion to the number of double bonds in the fat. A deficiency of polyunsaturated fatty acids is anti-estrogenic, partly by allowing the thyroid-stimulated liver to excrete estrogen, and partly by failing to activate the pituitary secretion of gonadotrophins.

G.W. Crile found that the basal metabolism of the people in Yucatan, where coconuts are a staple food, is 125% of that of people in the United States. Animal experiments show that coconut oil added to a normal diet can lower serum cholesterol levels. There is a very reliable inverse relationship between the level of serum cholesterol and thyroid hormone action. A major effect of thyroid is to control the conversion of cholesterol into steroid hormones and bile acids.

Thyroid promotes the formation of progesterone, which in turn promotes the secretion of thyroid hormones. Estrogen blocks their release from the thyroid gland, causing the gland to enlarge.

Iodine deficiency used to cause goiters in the United States, but now it is almost impossible to have an iodine deficiency in this country. Iodine supplements can suppress the formation of thyroid hormone, producing classical signs of hypothyroidism.

Hashimoto's thyroiditis is often diagnosed, without appropriate evidence. Even when correctly diagnosed, the knowledge isn't relevant to treatment. Thyroid cells contain estrogen "receptors," and estrogen inhibits thyroid secretion, and excess estrogen is involved in most "autoimmune" disease. Supplemental thyroid so easily normalizes estrogen and the immune system that it, with progesterone and pregnenolone and DHEA, should be considered as the cure for autoimmune diseases, including thyroiditis – at least until someone finds an "autoimmune" disease that doesn't respond to a balancing of these hormones.

Breast discomfort and even the secretion of milk not associated with pregnancy or parturition, produced by excess prolactin, can often be relieved by thyroid, especially when taken with vitamins A and E. The incidence of breast cancer is high in hypothyroid regions. Excess prolactin and excess estrogen are associated with each other, with breast cancer, and with hypothyroidism.

Most physicians know how to test the Achilles tendon reflex, but believe it is a poor indicator of thyroid function. Often, this is because they have observed the reflex contraction itself, rather than the relaxation rate, which gives a clear indication of the rate at which energy is regenerated in the muscle. The "T wave" or repolarization wave in the electrocardiogram gives a similar indication of lagging energy production in hypothyroidism. Magnesium retention by cells is dependent on thyroid hormone, and is essential for cell relaxation.

The rate of energy restoration is relevant to the tired brain, too. Insomnia is the most commonly troublesome symptom of menopause, and it usually responds immediately to a small bedtime dose of T3, just as T3 rapidly restores the normal quick relaxation rate to the calf muscles and heart muscle. (Two or three grams of sodium chloride taken at bed-time in a little broth, or juice or water, has a strong sleep inducing effect; it lowers adrenaline, promotes glucose absorption by the intestine, and has other antistress actions, including "sparing" magnesium.)

Thyroid permits energy to be produced efficiently from glucose, and hypothyroidism causes glucose waste leading to hypoglycemia, which in turn leads to excessive

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Thyroid Misconceptions

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secretion of adrenaline. Adrenaline, like the synthetic drugs that mimic its actions, has been known to be toxic for many years. It mobilizes fatty acids from storage, and its most obvious toxicity is to the circulatory system.

The circulatory complications of diabetes were avoided in Broda Barnes' diabetic patients, who received thyroid supplements. In diabetes, glucose is unable to enter cells, and the body's response resembles that of hypoglycemia, secreting adrenaline and mobilizing fats from storage. Since a certain amount of intracellular glucose is needed before the liver can form T3, diabetics, like hypoglycemics, or like anyone during starvation, are unable to activate the thyroid hormone.

Adrenaline secretion leads to cortisol secretion. The "Cushingoid" fat distribution, sudden balding, and other signs of hormone imbalance secondary to hypothyroidism are statistically associated with heart disease. Broda Barnes clearly showed the protective action of thyroid against heart disease.

Too much thyroid does cause enlargement of the heart. Meerson, and others, have shown that growth of the heart muscle is a normal process of adapting to an increased workload. In a more extreme situation, too much thyroid can cause relative starvation, arresting growth, by causing the tissues to "work" too intensely. When mice are given food containing 1% thyroid by weight, they stop growing, but normal growth resumes if they are also given liver as a nutritional supplement. Rats that were given enough Armour thyroid to stop their growth (up to 0.7% of their food) had bones that were slightly heavier than the bones of the rats on the normal diet that had grown at the normal rate. That is, even when the diet isn't adequate to sustain normal growth, hyperthyroidism doesn't necessarily cause osteoporosis. Very large doses of thyroxine, though, are not the same as hyperthyroidism. An often cited report on osteoporosis that was observed in a few women who were taking thyroxine, actually provided no clear data to support its conclusions, but it did illustrate two important fallacies: Failing adequately to take into account that women who take thyroid medication have a history of hypothyroidism, and ignoring that thyroxine reliably suppresses the pituitary TSH and thus decreases the T3 secreted by the thyroid gland, but doesn't reliably increase the liver's formation of T3. Hypothyroidism, whether natural or promoted by administered thyroxine, retards bone remodeling and tissue repair in general. As hypothyroidism predisposes to excess cortisol effects, it must also be a common factor in "Cushingoid" osteoporosis.

When the thyroid is normal, vitamin A and cholesterol are used rapidly in forming progesterone. Carotene tends to accumulate in hypothyroidism, and it can bind to the cells of the corpus luteum, preventing the use of vitamin A to form progesterone. Adrenalin, cortisol, prolactin, and ACTH are likely to be elevated in hypothyroidism, and they have been proposed as inhibitors of ovulation or progesterone secretion. Estrogen is usually elevated in hypothyroidism, and can prevent implantation of the embryo, or cause miscarriage if implantation occurs. Adequate thyroid normalizes these anti-fertility factors, which is why it was considered the basic fertility hormone. It is also essential for the vitality of sperm cells.

Animals which are artificially made hypothyroid develop cystic ovaries, so it is reasonable to consider hypothyroidism as an important factor when women have cystic ovaries. Thyroid hormone's effects on all systems of the body – nervous, immune, digestive, excretory, respiratory, etc. – contribute to optimal fertility, and to the vitality of the offspring.

Exercise lowers the level of thyroid hormones, partly by accelerating their breakdown. The stress of winter appears to do the same thing, and most people (and animals) need much more thyroid in the winter than they do in the summer. Exercise lowers human (and some animals') fertility, and winter lowers animals' fertility. I think human fertility, as indicated by sperm count, for example, is likely to be lower in winter.

Because some estrogen is secreted in the bile, adequate fiber in the diet (oats, potato, or raw carrots, for example) and regular bowel function help to prevent the build-up of estrogen, which inhibits the thyroid. (Estrogen which has been excreted in the bile can be reabsorbed from the intestine if there is slow transit time and too little fiber.) A deficiency of B vitamins or protein is also known to prevent the liver from excreting estrogen. One of the ways in which starvation inhibits thyroid function is by damaging the liver function. Vegetarians are sometimes dangerously deficient in protein, and in that state the body is very resistant to thyroid hormone. Elevated serum calcium is probably one of the factors in creating a state of thyroid-resistance during stress.

Thyroxine can protect against lipid peroxidation, yet the hormone is essential for the normal oxidation of fat. One aspect of its "antioxidant" function is that it allows respiration in the mitochondria to consume the reduced (electron donor) substances, which otherwise can accumulate and be oxidized by stored iron, to start the free-radical attack on lipids.

There are many directly anti-thyroid substances, but the only directly thyroid-activating substances I know of are coconut oil, progesterone, and pregnenolone. The saturated fatty acids, especially the highly soluble smaller molecules found in coconut oil, probably tend to simply dilute and weaken the inhibition that is chronically exerted by the polyunsaturated fatty acids, but butyric acid seems to have some specific effects, such as facilitating the uptake of T3 by nerve cells and shifting cells away from the expression of the stress-related proteins. Progesterone promotes the release of hormones from the thyroid gland, and by promoting the formation of glycogen, it probably supports the formation of T3 by the liver. Pregnenolone, which is formed from cholesterol in the mitochondria, also normalizes thyroid function, probably partly by optimizing the balance of steroid hormones, and partly by stabilizing the enzyme systems of the mitochondria.

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Transdermal Progesterone for Premenstrual Syndrome

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For many years, Katharina Dalton[1] has studied the use of progesterone therapy for the premenstrual syndrome. A typical patient may require ten or more progesterone injections per month, more or less permanently. While this is feasible (at least in some countries) it is not comfortable or convenient, in some cases leads to serious reactions at the injection sites, and in the United States would be too expensive for general use. When the syndrome is disabling, even the burden of frequent and expensive injections is usually seen a welcome alternative. However, a less expensive and more pleasant form of administration could make the therapy available to millions of women who are now disabled for one or more days each month. We are reporting here on what we believe to be a satisfactory alternative to the injection or implantation of progesterone, namely, a solution of progesterone and vegetable oil in a lotion or "cold cream" base for transdermal use.

After animal experiements revealed that progesterone in vegetable oil was absorbed effectively through the skin, in 1977 we began experiments with women who suffered from the premenstrual syndrome.

The effectiveness of the transdermal (absorption) route of administration varies with the individual, but compares favorably with injections in the amount assimilated. Thickness of skin or degree of circulation in the skin (these can be very abnormal in hypothyroidism, for example) and the amount of adipose tissue apparently make some difference in the rate of absorption and response. When a small daily dose (e.g., 5 or 10 mg.) is sufficient, this can be taken as about 250 mg. of a three percent cream rubbed into the throat, where it leave no noticeable oiliness after a few minutes. For large doses, the appropriate amount can be applied to a larger area of skin after a hot bath, once or twice a day if necessary.

We have used transdermal progesterone therapy in two hundred women suffering from the full range of premenstrual symptoms, including migraine, acne, depression, mastalgia, edema, and lethargy, and we found that nearly all of the women, applying the lotion themselves, are able to find the appropriate dosage for controlling their symptoms. Occasionally, thyroid therapy, weight reduction, or change in some aspect of life-style is necessary for complete relief from symptoms. We have learned that it is necessary to be very explicit in describing the amounts that can be used, while leaving it up to the patient to find the dose which controls her symptoms, because some women have an exaggerated idea of the power of a "hormone." We have learned, when some women said the progesterone had no effect, that they were applying it as sparingly as they would a rare perfume, just touching it to their wrists.

Another problem we have encountered is that a few women have trouble understanding how, if their edema is caused by "hormones," a "hormone" could relieve the edema. We have usually solved such problems by applying one dose (sometimes using a twenty-five percent solution) in the office, and waiting thirty or forty minutes to make sure that it was large enough to take effect. Once having felt sudden relief from this "cold cream," it is easier for the patient to understand how it should be used.

Unfortunately, many of the solvents which hold progesterone stably in a concentrated solution are highly allergenic. Injectable progesterone in oil could be used transdermally except for this problem. Progesterone can be removed from an injectable water suspension, and dissolved in warm olive or almond oil for transdermal use in patients who react to other solvents.

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Our research was supported by Blake College, Eugene, Oregon, and by Medical Diet Service, Inc., Portland, Oregon.

Ray Peat's Newsletter

Szent-Györgyi's Energy

A few years ago someone found that yellowing deciduous leaves in the fall were in the state of protein catabolism. I have discussed how this parallels the "toxic" effect of night and winter on animals; the darkness damages mitochondria, and red light seems to be the most effective frequency in restoring their function. The observation that cortisone begins to rise (in humans) when lights are turned out, rather than when people begin to sleep, nicely fits with the rabbit mitochondria studies, and the autumn leaves: either the cortisone causes the damage, or, more probably, the mitochondrial inefficiency wastes glucose, and increased adrenalin, cortisone – and dreaming – are responses to hypoglycemia.

At the moment I am working on the idea that potato plants, which do not normally produce seeds, can be induced to do so by blue (and other high frequency) light – at least when grown in acidic soil which provides iron or other heavy metals which tend to generate free radicals. This idea is a kind of generalization of the idea I first heard around 1953, from an old forester who knew that a coneless pine tree could be caused to produce a heavy crop of seed by injuring it with an ax. There are many other examples of the same process, such as grass which produces seed early when the weather is dry. The many toxic effects of estrogen caused me to interpret its effects (for example, rapid cell division in the uterus) as another example of the same process. In the 1940s, people often talked about famine causing extremely early fertility in girls; although it wasn't much discussed at that time, starvation (and other stress) does cause an elevation of estrogen.

Since Albert Szent-Györgyi died I have been thinking about his idea that the "Hopkins electron pool," stored in cellular proteins provides the energy for cell division. Around 1972, someone reported that sunlight shining on dark hair induces free radicals, and that these free radicals persist for hours in darkness. But exposure to red light "quenches" the free radicals within seconds.[1]

My idea of the "toxicity" of darkness is that free radicals (produced by metabolism, or maybe by cosmic rays) accumulate with time, but that the red component of light normally quenches them. In darkness, the excess of excited electrons would begin to spread beyond their safe storage system, and to cause toxic effects, such as oxygen wastage.[2] Many toxins and stressors are known to act through a common pathway of free-radical damage;[3] this accounts for the generalized protective effects of certain substances, such as vitamin E (as discussed by Meyerson in *Ray Peat's Newsletter* #29).

One of the most sensitive tests for estrogen's effect is the reduction of a dye (called TTC) by tissue and whole cells;[4] it is reduced (theoretically) by various "dehydrogenases." (The Hopkins electron pool was called by E. Racker "nothing dehydrogenase"). Progesterone blocks estrogen's effects on this dye. Since a similar dye has been used to measure the activity of superoxide dismutase (SOD), it seems that the superoxide radical can reduce the dye. Whatever the source of the electrons, estrogen and progesterone act in different directions on their availability.

Progesterone is known to inhibit cell division in various situations: in the uterine endometrium, in cancer, and in frogs' eggs. Several years ago, someone found that the progesterone in frogs' eggs was bound to the melanin – whose function in the eggs was never understood. (Though Szent-Györgyi for many years emphasized that pigments often exist invisibly inside organisms, and probably have electronic-metabolic functions, rather than the decorative function usually associated with pigments). Melanin generally exists as a complex with proteins. If the energy for cell division is stored in proteins, and if progesterone is acting on the eggs to inhibit cell division, and is bound to the melanin – which is known to store electronic excitation – then maybe progesterone is acting to prevent the escape of energy from the protein-melanin system.[5] If it does this generally, that could explain its very general "catatoxic" effects.

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Szent-Györgyi's Energy

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It was around 1954 that I first found some potato fruits, and hoped to get viable seeds with which to grow new strains of potato.[6] Around that time, John Ott found that squash plants he was photographing with pink artificial light produced only male flowers. The next season he used bluish artificial lights, and his plant produced only female flowers. Later, he found that night blooming plants such as the Morning Glory, could keep blooming if exposed to blue light, but when they were exposed to pinkish light their blooms collapsed.

All of this seems to be converging on the idea that the female reproductive tissues are activated by a free-radical or excited electron promitotic system. But beyond that it seems to have clear implications for aging, stress, toxicity, energy, tissue repair, regeneration, etc. The key idea is that biological structure and biological energy are delicately linked and balanced even at the finest – molecular and submolecular – levels.[7]

Notes:

1. Some people now consider melanin to be an anti-oxidant. It is important not to confuse melanin with lipofuscin, which is produced under oxidative stress and is able to accelerate the wastage of oxygen and energy.
2. Oxygen wastage itself will block respiration, disrupt mitochondrial function, and allow intracellular calcium to increase. There is clear evidence that many types of cell damage lead to cell death by a common "calcium path." Tissue stress has many self-promoting loops: enzyme release, formation of carbon monoxide and probably cyanide, retention of iron, etc. Sulfur, especially as the sulfane and sulfhydryl forms, is involved in many protective processes: see *Ray Peat's Newsletter* #5, 6 and 50. Deposition of calcium and iron are closely associated, and in oxygen deficiency iron becomes a major source of free-radicals, as discussed in *Newsletter* #41.
3. This pathway, according to Meyerson, is closely linked with the calcium-cell-death pathway; supplemental magnesium and vitamin E closely interact in protecting against stress.
4. Disruption of the cell destroys the ability to reduce the dye, suggesting that something more than ordinary enzymatic reduction is involved. At least, the phenomenon would involve an extreme sensitivity to concentration. This violates the basic assumption of conventional (and stupid) "test-tube biochemistry," namely, that reactions in the test-tube meaningfully reflect what occurs in the cell. Le Chatelier's principle "when a balanced system is disturbed, the equilibrium will shift in a way to restore the original condition," shows how complex enzymes can change activity upon dilution, but this is not generally thought to apply to the dehydrogenases.
5. In "A biophysical approach to altered consciousness" (*J. of Orthomolecular Psychiatry*, 1975) I proposed that a "leak" from this system could cause mental symptoms. Substances such as progesterone might have their beneficial psychological and neurological effects by stopping the leak.
6. In the winter of 1954-55 I experimented with growing algae under various lights – red, blue, and ultraviolet – to compare with algae grown in daylight, but I didn't have facilities for growing larger plants under those lights, and it has taken more than 30 years to get back to it.
7. Szent-Györgyi invented this field, called submolecular biology. It shades into Selye's "supra-molecular" biology through the work of many people, such as Gilbert N. Ling, F.Z. Meerson, and Otto Warburg.

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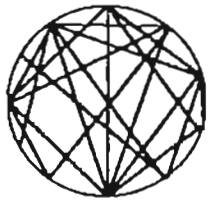

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We should remember that our cancer establishment, the alliance between government and the medical/pharmaceutical industry, has been claiming victory against cancer for several decades, while the death rate from cancer has steadily increased. This discrepancy between their claims and reality can be understood with the help of three facts:

1. By increasing the number of people diagnosed as having cancer, the "cure" rate can be increased. Every middle-aged person has some tissue that could be diagnosed as "cancerous." Soon, magnetic resonance imaging will be so sensitive that most of those "cancers" can be found, and the "cure rate" will rise to about 90%, but the death rate from cancer won't decline.

2. The baby-boom that followed World War II caused the rate of increase in cancer mortality to decline, because most cancer occurs in older people, and they were becoming a smaller percentage of the whole population. The same tricks used by the cancer industry could allow someone to claim that the "standard" lifespan was now about 92 years. Although this is statistical fraud of the crudest sort, it has been consistently accepted and promoted by university scientists of the "first rank," who benefit financially from the misrepresentation.

3. The same baby-boom caused an increase in childhood leukemia. At the same time, radiation from atomic bomb testing and prenatal X-rays caused a real increase in the risk of leukemia. The American Cancer Society used 1940 for "age-standardization" to make the general cancer rate look better, but they re-standardized when talking about childhood leukemia, so their calculations would show a downward trend. The downward trend in childhood disease was naturally produced by a declining birthrate, the end of the baby boom, but it was undoubtedly reinforced by the end of atmospheric nuclear testing and by the decreased use of prenatal X-rays. But these figures are the basis for the cancer industry's main claims of success.

Many poisons can cause tumors to shrink, and the yew tree contains such poisons. But shrinking a tumor has nothing to do with increasing a patient's survival prospect. The quack-busters have made that point many times in attacking "unproven cancer remedies."

At best, taxol is an unproven cancer remedy, but when a drug monopoly is promoting a new product, facts hardly matter.

The mechanism of taxol's cytotoxicity is probably similar to that of colchicine, namely, interference with the microtubule system. Microtubules are essential for cell division and many other cell functions. The goal of cytotoxic chemotherapy is to block cell division in cancer, without destroying cell division in essential tissues such as blood, the intestine's lining, skin, and the immune system. Certain cells of the immune system are uniquely fragile, and this fragility sometimes makes it possible to kill a cancer derived from those fragile cells, without killing the patient. The use of glucocorticoid hormones to destroy thymus-derived cancers takes advantage of that natural sensitivity and fragility.

Besides cell division, many (if not all) cellular functions depend on normal microtubule physiology. Microtubules are especially prominent in nerve cells. They are involved in axonal transport. It is not surprising that taxol is very toxic to nerve cells.[1,2] Microtubules are probably involved in the amoeboid movement of white blood cells, and taxol is very toxic to the neutrophils. Microtubules are involved in the fusion of their digestive enzyme vacuoles with their phagocytic vacuoles.[3] The neutrophils, effective tumor cell killers, would not be poisoned by a rational therapy. (These cells also govern wound healing and tissue remodeling, and I will discuss them later in relation to aging and regeneration.)

The metabolism of cholesterol into pregnenolone and progesterone (which are natural anti-cancer factors) is blocked by taxol.[4] Adrenalin secretion is also inhibited by taxol,[5] and adrenalin too, has some relevance to cancer control, e.g., it is anti-mitotic.

Certain cytotoxic treatments have a very rational basis. For example, cyanide poisoning followed by thiosulfate detoxification, is based on the fact that cancer cells consistently lack the enzymes for detoxifying cyanide by combining it with sulfur. Cyanide is too cheap to warrant serious consideration as a cancer therapy. (The pharmaceutical industry has undoubtedly considered promoting their cancer drugs to replace cyanide in capital punishment, but so far death by torture is acceptable only for cancer patients.) The established specificity of cyanide/thiosulfate toxicity for cancer cells contrasts with the generalized toxicity of taxol, which could be classed with whole-body irradiation as a desperate and irrational approach.

One aspect of taxol research might advance our understanding of the body's defenses against cancer. It happens that taxol, like bacterial endotoxin, stimulates macrophages to secrete tumor necrosis factor (TNF). This knowledge might lead to an insight into the nature of the process that controls TNF, and how that process fits into normal immunity. Promoting the body's natural immunity, combined with reducing our exposure to cancer-causing factors, should have higher priority in the health sciences, but the power of the drug industry focuses attention on the idea of medically killing cancer cells.

William McGuire (Johns Hopkins School of Medicine) reported in 1989 that 12 patients out of 48 with "refractory" ovarian cancer[6] "responded" to taxol treatment. All but two of the patients were dead by July, 1991. Ninety-six percent mortality doesn't sound very good.

A study at the University of Pennsylvania Cancer Center[7] found that, in patients with extensive malignant disease, there was no difference in survival time for patients who got conventional treatment, and 78 similar patients who were treated with unorthodox methods at the Livingston-Wheeler Clinic. A growing number of physicians recognize the uselessness of most conventional treatments.

A 77 year-old friend of mine had a physical examination, and learned that he had prostate cancer, though there had been no symptoms. As soon as he was given estrogen "therapy," he became miserable, and was never comfortable again, and died of a stroke a few months later. He believed that the misery was "extending" his life, because that is what his physician told him. There is clear evidence that estrogen does not prolong survival in prostate cancer patients, and the often cited "research" which is said to show the efficacy of estrogen treatment was nothing but a survey of doctor's opinions. The survey was done at a time when it was believed that prostate cancer is caused by testosterone, and that estrogen antagonizes testosterone. In fact, animal experiments show that estrogen causes prostate cancer, and *in vitro* tests show that it, but not testosterone, stimulates cell division in human prostate tissue. Progesterone, which antagonizes both estrogen and testosterone, has been used to shrink enlarged prostates, but estrogen continues to be used to treat prostate cancer.

If poisons are going to be used against cancer, they should be more toxic to the cancer than to the patient, and they should extend the patient's lifespan, and/or decrease suffering.

A very competent cancer researcher found that the patients who delayed longest in going for medical treatment for cancer had the longest survival. If patients would remind their doctors to "first do no harm," there might be fewer lives lost in the heroic "war against cancer."

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Ray Peat's Newsletter

The Edema of Stress

Our medical culture is bloated with retained errors – especially in connection with tissue water and its regulation. Sometimes, just by finding and eliminating errors, a new pattern will reveal itself in the remaining data.

A popular laboratory assignment for students in physiology is to drink a liter of ordinary or distilled water, and to measure the urine output in the next few hours. Then, in the next class (or with different students), a liter of water with 9 grams of sodium chloride is drunk. The urine output over the next several hours is about a liter less than in the first experiment. Thus, "sodium causes water retention." Textbooks base everything on this simple idea that "water follows sodium." "There are," they say, "no water pumps, only sodium pumps in cells."

Two real-world observations reveal the nature of the mistake in that doctrine.

People who work hard in the summer have noticed that their sweat can be so salty that it leaves salty crystals on their hair, and burns their eyes. They may need salt tablets during the day to keep from fainting. But other people, on a low salt diet, can sweat copiously without losing much salt. The body obviously adjusts its salt retention to compensate for salt intake.

By experiment, this adjustment takes only a couple of days. If physiology labs extended their experiments, they would find that sodium does not cause water retention in any sense that matters physiologically. In fact, in both animal and human studies, there are situations in which increased sodium helps to unload excess tissue water.[1]

The second real-world observation is that millions of women (in my direct observation, several hundred) have severely restricted their salt intake, yet continue to suffer from cyclic edema. Because of the assumption that "water follows sodium," and that body fluids are "isotonic" (with "isotonic" salt solutions, or with intracellular fluids), people seldom measure the osmolarity of blood plasma or serum. Estrogen causes the retention of water independently of sodium, causing the molarity of the plasma to decrease. Uremia and, in general, old age cause the molarity of the blood to increase.

Seeing that salt restriction never helped women with cyclic edema, I explained the mechanisms of water regulation, first to just one woman. Within a month, she was salting her food to taste (i.e., salting it heavily in the premenstrual week), and having no trouble with edema. Since then (1978) I have explained this to many women, and it always works for estrogen-induced cyclic edema, and also for the edema of pregnancy induced by excess estrogen,[2] and for the occasional older person for whom it seems appropriate.

Serum albumin with its associated sodium ions, exerts a colloid osmotic pressure which is important in holding water inside blood vessels. Without its associated sodium ions, its intravascular effect is weakened, while the sodium-deficient water tends to cause cellular swelling.

Swelling of tissue cells is the kind of edema which is a serious problem in brain injury and stroke,[3] as well as in traumatic or toxic injury to other tissues, and whenever there is an inadequate supply of energy to cells,[4] as in hypoxia. At a certain point, the resulting pressure of swollen cells outside capillaries can no longer be compensated by adjustments in the blood vessels and increased blood pressure, with the result that tissue perfusion, nutrition and oxygenation are insufficient. (Thus, a severe sodium deficiency contributes to cellular hypoxia).

When cells can't maintain their energy, they swell if exposed to a standard osmotic environment. This is the ordinary "edema of hypoxia," which is similar to the swelling of cells in tissue culture in "normal isotonic medium."

The conventional story to explain this swelling of hypoxia is that the "sodium pump" requires energy to keep the sodium out, and that inadequate energy allows water to "follow the sodium" into the cell. This explanation is wrong and misleading. While energy deficiency causes cells to swell abnormally, water is also *retained* by normal cells under the influence of energy. Much of the cell's energy, in the form of protein-bound ATP, regulates the colloidal nature of the cell, including its water content.[5] In this well-tested view of the cell, it would be appropriate to say that "sodium follows water," to contrast its medical implications to those of the "sodium pump" theory, and to create an image of the potentially protective function of sodium.

The generalized edema of hypoxia is closely related to the focal edema which occurs in inflammations and cancers.[6] In a focus of inflammation, the local metabolism, especially of glucose, increases

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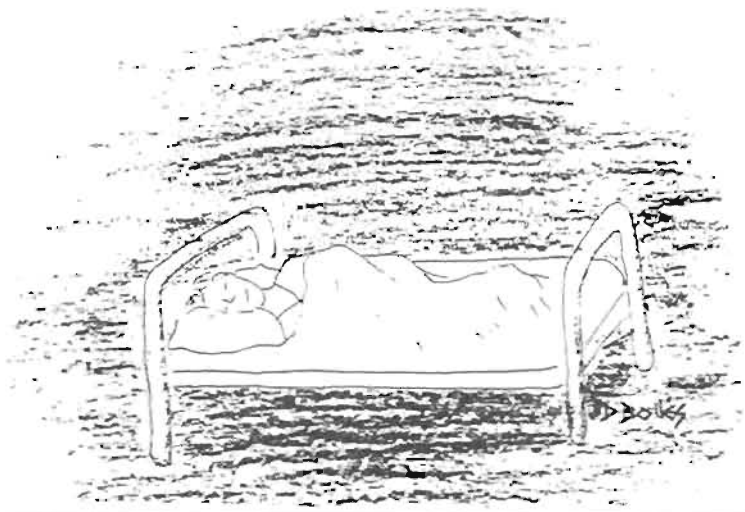
(1)

Further Adventures of Dr. Herbinski

Content in the knowledge of giving love, health & organic happiness to his patients for another day, Dr. Herbinski peacefully retires to the Freudian Netherland.



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to compensate for a loss of energy. (In a cancer cell, glucose consumption is often several times higher than that of a muscle cell in maximal activity). The focus becomes acidic. The provoking stimulus causes the ATP-protein complexes to break down, with production of ADP and phosphoric acid, and with changes in protein conformation. The increased dispersion of colloids, and the concentration of metabolites such as lactic acid, ammonia, ADP and phosphate, increase the osmotic and oncotic pressure of the cells. The osmotic pressure can be twice normal.

As early as 1920, there were studies of the extremely high osmotic pressure of serum from uremic patients. If there is systemic hypoxia, this very high osmotic pressure of the blood can be seen as a lucky – or adaptive – defense against the tendency of tissues to swell. Circulation can be maintained under conditions which otherwise would cause tissue swelling and compression of capillaries. Urea is used as a "diuretic" to treat edema of the brain in some circumstances, but it should probably be used more often. A small amount of DMSO (e.g., 1 1/2%) similarly causes cells to shrink.[7] This would seem to explain much of its anti-inflammatory action (yet the doctrine of "membrane pumps" says that permeant solutes shouldn't cause cell shrinkage. The use of hypertonic urea[8] or DMSO, or glucose (about 400 mg. per deciliter, for example[9]) to treat cancer would help to restore circulation, prevent the adaptive leakage of proteins from cells, and allow normal regulatory processes to function more efficiently.

Serum albumin is one of the body's most powerful tools in maintaining homeostasis. Gilbert Ling has demonstrated that serum albumin or collagen, when "denatured" by urea, has a greatly increased oncotic pressure, or tendency to retain water.[10] Under physiological conditions, it is probably a variety of solutes, especially free fatty acids, which cause albumin to adjust its oncotic pressure.

I think the extremely quick changes that sometimes occur in extracellular connective tissue substance (e.g., in arthritis, exophthalmia, or glaucoma) in response to progesterone, pregnenolone, DHEA, or other related steroids, are likely to result from a similar physical effect on the colloidal osmotic pressure of the body fluids, and possibly of the connective tissue substances themselves. Diffusion of oxygen through the lungs can be obstructed by layers of colloidal material, and steroids are involved in mitochondrial structure and stability and other cellular processes, so I don't mean to deny that these hormones also have other powerful effects, just that some early effects in relatively inert tissues are so quick that shifts in water content seem to be the best explanation.

Knowing that old organisms are relatively dehydrated, it is interesting to see that when a young muscle is made to lose some of its water, it functions similarly to a muscle from an old animal.[11] Recently, enzymes from old animals were denatured, causing them to lose their specific folded arrangement. When they were carefully "renatured," it was found that their enzymic function had increased, to become the same as that of enzymes from young animals. This shows that the nature of the "solution" in the cell, the conditions under which the enzymes are synthesized, has subtly modified their shape. Restoring the cell's energy, which governs the cell's colloidal state, might be able to restore all cellular functions to the active, young state, though this state would have to be maintained until protein "turnover" had renewed a large part of the cell structure. ("Protein turnover" refers to the normal process of renewal, in which some proteins are destroyed while new ones are being made).

Energy, in the form of ATP with magnesium, can be effectively supplied to tissues through the blood stream.[12] (Again, it has been the dogma of the "semi-permeable cell membrane" which has blocked the acceptance of this work: ATP simply couldn't get into cells, they said).

Energy, produced under the influence of the thyroid hormone (triiodothyronine, T3), and acting to eliminate edema, can correct many problems that don't seem to have anything to do with "energy." The carpal tunnel syndrome, involving swelling in or around nerves, is often relieved by a thyroid supplement, or by avoiding anti-thyroid foods such as beans and seed oils. (Surgery to relieve the pressure caused by swelling is the conventional treatment). Several people with a diagnosis of "multiple sclerosis" recovered immediately and fully when given thyroid. (Triiodothyronine does influence myelination,[13] but I think the important causal sequence is: first, disturbed respiration, then edema, then demyelination).

Many animal diseases, produced by copper deficiency and its associated respiratory defect, involve swelling of the brain and/or spinal cord. Dogs, horses, and sheep develop weakness or paralysis of the hind legs, as a result of compression of the edematous spinal cord. In chronic copper deficiency, cells absorb an excess of iron,[14] so treatment isn't just a simple matter of giving supplementary copper. Hyperosmotic therapy, to directly relieve the swelling and restore circulation, would probably have to be the first step. In treating either hypoxia or iron-overload, there is the danger of tissue injury from the free radicals produced by reduced iron.

There are many practical, simple consequences of recognizing the interactions of osmotic pressure, metabolism, and inflammation. For example, people with inflammation of the bowel, resulting in obstruction that can't be relieved by an ordinary enema, have found that a hyperosmotic enema (sometimes with aspirin added) can relieve the edema which is causing the obstruction.

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Peat, R. (1991). The Generality of Adaptogens. *Townsend Letter for Doctors & Patients*, (100), 930. Retrieved from EBSCO*host*.

The Generality of Adaptogens

There are far more sensory nerves entering the brain, than motor nerves leaving the brain. Generalization and judgment intervene between the complexity of sensation and the coherence of behavior. Encountering an infinite world, we marshall our resources for an adequate response. For me, this "sensory domination" of the brain is an important metaphor that offers some insight into other systems, because it suggests that interesting events of integration might be happening "above" the easily observable mechanical behavior of a particular system that we are trying to understand.

To bring generality to the understanding of cellular resistance, we should look for events that commonly occur during successful or unsuccessful responses to stressors of various types. Several years ago, someone found that a "final common pathway" of cellular death was the absorption by the cell of a large amount of calcium, when the cells were injured in a variety of ways. Working with the stressed heart, F.Z. Meerson spoke of the "calcium triad," suggesting that there are ways to interrupt the progress of cellular death even after it has started. Calcium activates proteinases, phospholipasis, ATP-ases, contraction and oxidative peroxidation, and uncouples oxidative phosphorylation, so that numerous drugs can interfere with various aspects of the cellular death process after it has begun. Knowing that calcium is a normal activator of muscle contraction and other normal processes, we can consider the normal physiological controls over calcium, as places where a little extra support might keep our cells safely away from the "final common pathway" of cell death.

In different situations, we can see different components of a "terminal" process. For example, iron tends to accumulate with age, and areas of calcification in soft tissue typically show iron associated with the calcium. (This association is probably both physicochemical and pathophysiological.) Vitamin E is protective against the lipid peroxidation induced by iron,[1] as well as that stimulated by calcium. Mice killed by a variety of methods show a high level of histamine in their tissues, suggesting that histamine might be involved in a "terminal pathway" on either the organismic or the cellular level. Histamine can stimulate the entry of calcium into cells.[2] On the organismic level there are hormonal changes that accelerate the progress into a terminal state, and several of these are closely associated with the metabolism of calcium (cortisol, prolactin, and estrogen). Others are associated with the suppression of thyroid function.

Adaptogens are chemicals which increase an organism's ability to resist stress without suffering cumulative damage. This is a useful definition, since it excludes the glucocorticoids, which promote adaptation and short term resistance to stress, but do so at the expense of the organism's future reserves. Every aspect of our normal resistance that precedes our resort to cortisol can

suggest possible classes of adaptogenic substances to strengthen those functions. The avoidance, binding, and detoxifying functions are all part of adaptation, but the most important aspect of adaptation is the ability to maintain a high level of tissue energy, and the stabilization of respiratory energy production is needed for that. Besides the oxidative production of energy, we need to prevent the wasteful expenditure of energy, and this requires the ability to raise thresholds to stimulation. (We can see both of these processes working in the adaptation of a healthy child to a serious infection: having a fever, and sleeping.)

As soon as something interferes with the oxidative production of energy (not having enough oxygen, for example, as when running) we adapt biochemically first by increasing the consumption of glucose for glycolytic energy production. This increased consumption of glucose tends to lower the concentration of glucose in the blood, and this (or various other signals, such as pain or fear, that are associated with the need for more glucose) causes the secretion of adrenalin, which can mobilize glucose from the liver's glycogen stores. If the glucose stores are depleted, the body resorts to the secretion of cortisol, to provide glucose (and other material) by cannibalizing protein from tissues which are momentarily less essential.

Both adrenalin and ACTH mobilize fat from storage. Stress-mobilized fatty acids contribute to the increased lipid-peroxidation seen during stress, and they also tend to damage mitochondria. The large increase in the death rate from asthma in the last decade or two is now believed[*] to be the result of cardiovascular damage caused by the common use of inhalants containing catecholamines. Isoproteron01, a commonly used bronchodilator, causes mitochondrial damage, which can be prevented by blocking the carnitine-dependent oxidation of fatty acids. Since carnitine is required for the oxidation of long-chain fatty acids, its analog-betaines (which interfere with its transport of fatty acids into the mitochondria) protect against the damage that normally results from stress-induced (or catecholamine-induced) fatty acid oxidation. Since saturated fats protect against the cardiac necrosis produced by corn oil, I think it is probably lipid-peroxidation resulting from rapid oxidation of unsaturated fats which causes the heart damage in both catecholamine damage[3] and corn-oil toxicity. Vitamin E, coconut oil, and the carnitine antagonists (betaine derivatives) are adaptogens that protect respiration by directly decreasing lipid-peroxidation.

Uncompensated stress or injury is a complex process, so it shouldn't be suprising that adaptogens have a "broad spectrum" of beneficial biological effects, but it is precisely the breadth of vitamin E's effect that have made many physicians reluctant to use it, because they are trained to think in terms of "lock and key" specificity in pharmacology. The same reaction can be expected from drug-dominated medicine, as results with other adaptogens are published. For example, a Soviet adaptogen of the betaine class which is used as a feed-additive for animals, has been reported:

to induce interferon and protect against influenza virus,

to protect the brain against hypoxia, to promote healing of wounds, burns, and sores,

to activate immune responses,

to promote cell division in thymus and spleen,

to restore contractility to hypoxic heart tissue,

to increase the contractile capacity of the heart by increasing ATP concentration,

to prevent decrease of ATP levels under various conditions,

to reduce isoproteronol or catecholamine-induced myocardial injury,

to protect the heart against fatty diets,

to promote methylation of chromatin proteins,

to promote reparative and replicative DNA synthesis,

to increase translation of nucleic acids (protein synthesis),

to stimulate the rate of growth in chickens,

to have very low toxicity, and

to be suitable for use in treating a wide variety of cardiovascular diseases, such as cardiac insufficiency, myocarditis, cardiosclerosis, ischemic heart disease, and arrhythmias of varying etiology, and to have long-lasting positive inotropic effect, and cardiac-dilating activity. [Literature search by P. Hockstaff.]

Since the substance seems to be a natural plant growth regulator, and to be cheap to produce, it is probably going to meet serious resistance from the drug industry/FDA monopolists, though the meat industry is likely to eventually find that it replaces many of the toxic chemicals that are now used.

The adaptogens of Eleutherococcus and ginseng are already in wide use. It is assumed that their steroidal components support the functions of our own protective steroids. These functions (normally adequately sustained by our endogenous steroids) are probably catatoxic, anti-catabolic, anti-inflammatory, and osmoregulatory. Since there is so much talk about catabolic or anabolic steroids, it's important to say something about the anti-catabolic aspect of the protective or adaptogenic steroids.

On a time scale longer than that of the immediate stress experience, preventing cumulative damage is just as important as blocking the immediate injury process. Since cortisol, which is life-saving on the short time scale, is a major cause of cumulative damage to the organism, it is important to investigate things which will limit its chronic catabolic effect.

Although testosterone is very catabolic for the thymus gland, it is anabolic for muscle, and there is some evidence that it is directly competitive with cortisol, which is catabolic for muscle. When radioactive testosterone was injected into a person, the experimenters were surprised to find that its main concentration was in the heart muscle, rather than in the skeletal muscle. This high

concentration of testosterone in the heart muscle suggests that an antagonistic relationship between testosterone and cortisol is responsible for the ability of the heart to retain its protein while starvation or stress is causing protein to be removed from skin muscle, thymus, and other tissues, under cortisol's influence. Such an "anti-catabolic" effect must be especially important during the years of growth, so the youth-associated steroids (prenenolone, progesterone, DHEA) probably serve in this way, while being available for conversion into the more specific hormones. Plant steroids such as those in ginseng, having some structural similarity to the normal protective hormones, would serve as adaptogens by making up for a reduced amount of those normal youth-associated substances.

Filatov found that stressed tissues of both plants and animals produce protective and stimulating substances, which can be extracted for medical use. He identified succinic acid as a component of his extracts. Szent-Gyorgyi found that succinic acid stimulates respiration, which might explain why it promotes synthesis of pregnenolone and related steroids. It and fumaric acid are now considered to be adaptogens. Since succinic acid safely chelates toxic heavy metals out of mitochondria, it might also safely carry copper into the mitochondria. Succinic acid is also closely associated with GABA metabolism (gamma-amino butyric acid is converted to succinic semialdehyde in a transamination reaction), and so is probably complementary to the GABA analogs GHB (gamma-hydroxy butyrate) and its lactone (which has anti-viral activity). GABA analogs are now one of the most actively studied classes of adaptogens. GABA has a wide range of stress-blocking actions, including neural inhibition, progesterone promotion, and blood sugar regulation.

The "local anesthetics," which generally have a broad range of effects, are an important class of adaptogens. Procaine has been found to normalize almost every system studied.[4] Doses far too small to have an anesthetic effect have clear biological effects. Lidocaine is used to prevent heart arrhythmia, and acts partly by preventing excessive calcium uptake by the cells. The atropine family of drugs is structurally similar to the "local anesthetics," and also have a long history of use in treating sickness and stress. Most of these chemicals have anti-histamine actions that are probably relevant to their value as adaptogens. These chemicals can protect microcirculation against spasms produced by exhaustion or overstimulation. Light can also have this effect.[5]

Promotion of synthesis and stabilization of the detoxifying enzymes is another function of some adaptogens. The catatoxic steroids do this, but since they also have an immediate protective effect (that could hardly involve the production of new enzymes), they probably have other mechanisms of action, such as improving the capacity for binding toxins of proteins such as albumin. Since even cholesterol has catatoxic action, I often advise people to eat more eggs for a variety of problems. The egg lipids (including phospholipids and cholesterol) enter the blood in microscopic particles, called chylomicrons. Synthetic "liposomes" are a pharmaceutical fad, promoted for their ability to transport various drugs, but the liposomes themselves (made from egg phosphatidylcholine and cholesterol) have anti-inflammatory and anti-bacterial actions. ("Anti-inflammatory action of liposomes," V.M. Kreys, et al., Vestnik Akademii Meditsinskikh Nauk no. 6 June 1990, pages 44-47.) I think we have to include dietary eggs in our list of adaptogens.

I have often described the thyroid hormone as the basic anti-stress hormone, because it is essential for respiratory energy production.[6] The ATP produced under the influence of the thyroid hormone binds magnesium, and is relatively stable in its presence. ADP, the lower energy phosphate that results when ATP loses one phosphate group, happens to bind calcium. Thus, the high energy state of the cell binds magnesium (when it is available), and the low energy state binds calcium. Many of the events that are said to involve "ion pumps" are just different "ion-binding states" of the cell. Both thyroid (to form ATP) and magnesium (to stabilize ATP) are essential for cellular resistance to stress.

Magnesium-ATP, and liposomal-ATP administered intravenously have been used successfully to treat shock and to restore mitochondrial function, and are undoubtedly powerful "adaptogens," but it is much more practical to ingest eggs, magnesium-rich foods, and a little thyroid, to get "cholesterol-liposomes" and magnesium-ATP. Creatine phosphate, which is normally an intra-cellular energy reserve in balance with ATP, has been found to prevent the heart damage caused by catecholamines.[7] Energy depletion (ATP and creatine phosphate) is probably the central event which precipitates the entry of excess calcium into the cell.[8]

Since many of the biochemical changes in aging are the same as those occurring in stress, the adaptogens tend to relieve the symptoms of aging. And to some extent, relieving the symptoms of aging tends to resist the forces that would otherwise push cells toward the "final common pathways." But the perfect adaptogen would be something that systematically blocked the agents of damage before any damage had been done. The avoidance of toxins and other stressors (including darkness) should be taken care of before too much emphasis is put on the use of adaptogens. Substances that have one clearly defined adaptogenic function often turn out to have several useful functions. Caffeine, for example, promotes thyroid function, blocks both radiation and chemical carcinogenesis, and inhibits absorption of iron, which under stress has important dysadaptive function.

Filatov's approach, using complex extracts of stressed tissue, suggests that certain methods of food storage and preparation might increase their adaptogen content, e.g., broccoli stored in a refrigerator has much more vitamin C than fresh broccoli; cold-dark storage was one of the stressors Filatov used. The same principle might apply to the use of crude plant or animal drugs. Traditional foods used for convalescents might also include some empirical adaptogens - broths, egg-nog, fruit juice, custards, etc.

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Notes

[*] Of course, the now discontinued use of sulfite preservative (approved and required by the FDA) in asthma drugs contributed to that high mortality.

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By Raymond Peat

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RESPONSE TO RECENT POP-MEDICINE ARTICLES ON PROGESTERONE THERAPY

R. Peat, Ph.D., Deming, New Mexico

Since 1940, it has been clearly established that estrogen is carcinogenic in every species studied. Shortly thereafter, studies appeared suggesting its possible involvement in heart disease. In 1950, I heard physicians warning about the risk of cancer when estrogen is used medically. The increased use of estrogen in the face of such evidence is, I believe, a process unique in medical history and is nothing but shameful for all who are involved.

By 1950, many studies had demonstrated that progesterone can protect against the effects of estrogen, including cancer. By that year, progesterone was shown to prevent estrogen-like and testosterone-like actions. Often, they suppress the formation of progesterone in the body, and in such cases could be called "anti-progesterone progestational agents." There is no justification for confusing progesterone with any synthetic steroid. When someone with access to the data confuses them, we must suspect their motives or their qualifications.

Progesterone has a unique position in physiology, partly because of its intrinsic range of hormonal activity and partly because it serves as a precursor for all the other types of steroid hormones. The concentration of progesterone which occurs during pregnancy is uniquely high among all hormones and requires a balance of intrinsic properties such that the physiology of the organism is protected, rather than thrown out of balance, by such high concentrations.

In spite of the toxic effects of even natural estrogens, multiparous animals and humans have a lower cancer incidence than do nulliparous individuals and apparently a longer life expectancy. These effects have all been related to progesterone.

Opponents of progesterone therapy are searching for new strategies, in addition to the standard "it's all in her mind" approach to women's symptoms. The ideology that pregnancy is a disease is being brought into service in this new conflict — women are being threatened with the thought that progesterone will make them feel pregnant, as if healthy pregnancy should cause undesirable feelings. One of the oldest warnings, and probably the most interesting, is that progesterone can produce feelings of euphoria. Less amusing is the totally false new threat that women may become progesterone addicts.

Reading some of the anti-progesterone literature gives one the impression that many doctors are suddenly going to reject the use of any medication which requires the adjustment of dosage to suit the patient's response. After discussions of how unscientific it is to use progesterone in dosages varying between 200mg and 2000mg per day, a writer in *Medical Month* (February 1984) says that: ". . . Absence of standard dosages troubles observers on both sides of the therapeutic fence. 'It's trial and error,' says Nathan Kase."[1]

Just to the left of that quotation, there is a half-page advertisement for a tranquilizer, saying "Trust Tranxene," which comes in scored tablets of 3.75mg, 7.5mg and 15mg, and in 22.5mg "single dose tablets." A scored tablet of 3.75mg suggests a possible dose of less than 2mg, and a "single dose" 22.5mg tablet indicates a dose about twelve times larger. This article, "Dangerous Fad Therapy for Premenstrual Syndrome?", defines progesterone as "cholesterol derivative," very likely to get a little extra propaganda value from associating it with the cholesterol scare. In fact, all natural steroid hormones are derived from cholesterol. (I wonder how such a sleazy article as this finds its way into physicians' waiting rooms.)

A new pseudo-medical campaign is under way, against the use of natural progesterone therapy in premenstrual syndrome. This campaign is likely to intensify as new, efficient and effective forms of progesterone become available.

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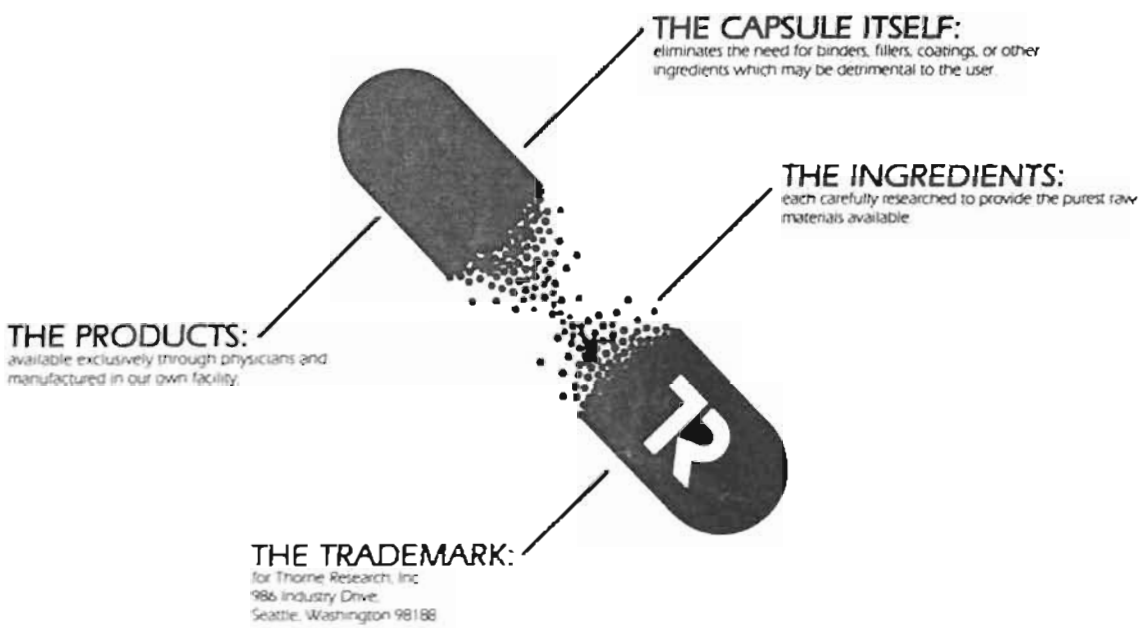

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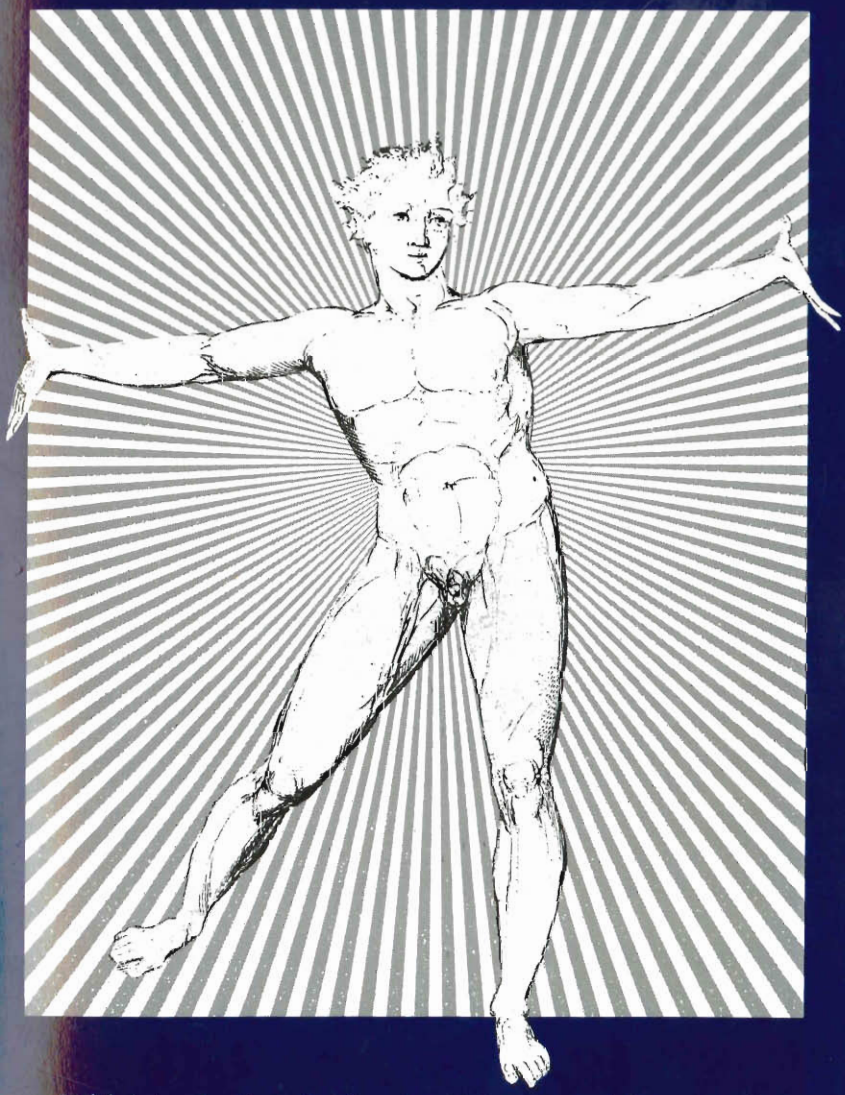
MIND AND TISSUE:

Russian Research Perspectives on the Human Brain

Raymond Peat, PhD



With introductions by Stanley Krippner and Peter Marin

MIND AND TISSUE:

Russian Research Perspectives on the Human Brain

By Ray Peat, PhD

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INTRODUCTION
By Stanley Krippner, PhD

The importance of contemporary Soviet psychology has been acknowledged by many authorities. Gardner Murphy and J.K. Kovach, in the third edition of their book, *Historical Introduction to Modern Psychology*, take up this issue. Speaking of psychology in the U.S.S.R., they describe "the magnitude of its existing and potential impact on the entire body of modern psychology...," stressing the point that "Soviet psychology is not a closed system."

These points are reinforced in *Mind and Tissue*. Its author, Ray Peat, has presented a cogent summary of Soviet psychology, highlighting the contributions it has made to our understanding of human behavior. Peat traces the philosophical origins of Soviet psychology as well as the tradition afforded by Dostoyevski, Tolstoy, and other writers.

The gargantuan contributions of Pavlov are described, beginning with the differentiation of the "first signal system," of sense perception from the "second signal system" of language. Ray Peat then emphasizes a point often ignored: Pavlov took the position that the whole organism had to be the subject of scientific study. Since presumably it is the whole organism which is conscious, a psychology which studies isolated behavioral reactions can easily avoid a confrontation with the issue of consciousness. This was not true of Pavlov, who advances ideas concerning sleep, dreaming, hypnosis, and imagery which contributed to our understanding of human abilities.

Pavlov's successors continue to study brain function, observing that plasticity is the outstanding property of the nervous system. This viewpoint is an optimistic one as it

gives parents, educators, and rehabilitationists a chance to develop those in their care by paying attention to the "latent reserves" of a child, student, or patient.

The reader of *Mind and Tissue* will enjoy the special discussion of such Soviet psychological concepts as "inhibition," the "orienting reflex," the "effect of person," the effects of magnetic fields on behavior, and the notion of time as a possible source of "energy." The current enthusiasm among some American psychologists for explaining behavior through differences between brain hemispheres could be moderated by examining the Soviet work on cerebral function which emphasizes a more holographic approach. In addition, the Soviet delineating of mental imagery components (space, body awareness, sequencing) leads to an emphasis on meaning and experience in describing brain function. Indeed, it is easy to follow the historical thread that links Pavlov's hypotheses on mental imagery with Lisina's pioneering work in biofeedback. Additional work in what the Soviets call "psychic self-regulation," has been done at Kazakh State University; practical applications of this work are to be found in many Soviet clinics and hospitals.

Finally, psychology in the U.S.S.R. views creativity not as a psychosexual sublimation or a lack of proper social conditioning but as an essential human trait, part of the need for self-realization through productive work. There is a richness in Soviet psychology that is often overlooked by American scientists. Ray Peat's assertion that materialists emphasize change while idealists emphasize the status quo may well be true. If so, it confirms Murphy's and Kovach's description of Soviet psychology as an open rather than a closed system.

INTRODUCTION
By Peter Marin

In its quiet way, this book is both a revolutionary gesture and a redemptive one. It is revolutionary because it liberates the mind and imagination from the habitually diminished ways we think about both self and world, and it is redemptive because it restores, at the same time, the detailed complexity of both realms. It not only gives us a way to judge the limits of our working views of human nature, and opens up avenues of speculation now closed to us, but it also weaves together psychological, biological, political and poetic truths, thereby releasing back into the totality of experience our idea of the self, now isolated from it.

I hope that comes clear in the course of this introduction and in the text itself, because what the text offers is precisely what we need at the moment: a complex and holistic way of coming to terms with our own complexities and momentary sense of fragmentation. For decades now the ways we think about both self and world have been dominated by a mechanistic and solipsistic view of experience, one riddled by a set of preconceptions owing more to our political and economic biases than to a close observation of our own humanity. At the moment we peer at ourselves in a mirror distorted by historical forces at work in our own consciousness: a set of preconceptions so deeply imbedded in our language and thought that we mistake them for the nature of reality itself. Or we develop, as an alternative to that, simplistic or mystical notions about things, hoping vainly through that device to restore to ourselves the world we sense to be missing.

Mind and Tissue is meant to be an antidote to both conditions: to free the imagination through fact and theory, to restore to us--in all its facticity and complexity--the parts of the self and world now missing from our psychologies. To do that, Ray Peat relies largely upon certain trends in Russian psychology and biology, especially those dealing with Marxist notions of freedom, consciousness and the interpenetration of subjective consciousness and the objective world. The Russians peer into a mirror altogether different from ours, one obscured or distorted by different prejudices, and that often allows them to confront or admit what we miss. They are looking for different things, working out a different version of human nature and human possibility, a different kind of faith in reason, will and desire (forces we tend to ignore in our own psychology), and for that reason the complexity of the problems they have chosen to examine and the elegance of their tentative solutions often puts to shame our own approaches.

Of course the Russian scientists named here do not necessarily represent the general drift of Soviet science. They are part of what one can call a "countercultural" science: an anti-bureaucratic, Marxist psychology directly related to the radical anti-bureaucratic trends in Russian thought which surfaced after the revolution before disappearing with the hardening of official state policy. In some ways, it is a more humane tradition than our own, closer to the kind of "humanism" we like to claim as our own. But there are also in it elements totally alien to us, most notably the willingness to accept, as an irreducible part of experience, the aspects of human nature we deny or explain away: passion, desire, imagination, the need for freedom, the relation of vision to action. Those have traditionally been the provinces of our literature rather than our sciences, but even there, in most of our contemporary

work, the willingness to deal fully with those questions has been less evident than it used to be.

That fact, and its consequences, grow increasingly clear as one reads *Mind and Tissue*. Ray has used the Russians to show just how impoverished our own views are. Where we say "ego gratification" or occasionally "pleasure," they are able to use a deeper, richer word, desire, to indicate not only a greater intensity of feeling than is present in the other words, but also to suggest a different relation between self and world, and interpenetration, a reaching out, a kind of appetence. In the same way, *freedom* for them exists not only as an ideal or a legal abstraction, but as a condition of being, a transformative and essential state they examine as carefully as we examine pain and pleasure. Somehow their work seems bigger and deeper than our own, and that should perhaps be no surprise, for it is deeply connected with their literary and political history, in which the state and nature of the soul--the inner and absolute identity of the person, the teleological nature of existence--have been as important as concerns as the social surface of behavior. Perhaps the most revealing single thing in the entire book for me, as a writer, is the credit given by Ukhtomskii, a leading Soviet theoretician, to Dostoyevsky, and his willingness to investigate Dostoevsky's visionary notion of *the double*. It is there, at the point that great literature and science coincide, that one feels the human being made whole again, as if we were seeing ourselves for the moment with a depth equal to the depth of experience itself. And the same thing is true, of course, for Ray's continual references to Blake, who he recognizes as the west's foremost psychologist. Blake's insights, like Dostoevsky's, remain the touchstones by which we must measure our theories of the person, for their task, as writers, was to delineate the complexities and

lineaments of experience, just as ours, as theoreticians, is to explain that complexity without diminishing it.

Implicit in the scientific use of a literary insight is the necessary modern reintegration of modes of thought which were once interdependent but are now treated separately. Philosophy, psychology, biology, politics, history--when one reads Kant or Rousseau or Hobbes or Marx one sees instantly the ways in which these varied concerns were interdependent, and that they understood that the truth of human nature could be found only in a vision which drew from and made whole again a variety of realms. Nature and the way we see it, as Ray knows, defines for us the way we act in history, just as history, in turn--the age we inhabit, or momentary consciousness--defines what we can see of nature, what it becomes.

It is necessary to put that into perspective before one can understand the implications of what Ray is trying to do in his book. Since the Enlightenment, modern consciousness in the west has been defined and in some ways directed by the human view of nature and human nature. Since then, when the human world began to replace God and Eternity as the center of concern, the changing ways in which we perceive ourselves have demanded, with each change, a corresponding change in social theory and social conditions. Each of the great waves of revolution during the past three hundred years has been preceded by a revolution in though and perception. At work in each wave has been a vision, or re-visioning, of human nature which creates, in the imagination, a necessary impulse and basis for action. In general the process has been one in which the power once ceded to God (and to kinds and priests, the hierarchical authority divinely sanctioned) was taken into the human world, understood as human power.

One sees that first at work in Rousseau and his contemporaries. The history and nature of humanity are perceived in an entirely new way. A "natural history" of the social past becomes the basis for the legitimization of revolutionary ideas. Not only is authority denied its divine origins (which are replaced by the assent of a general human will), but human needs are understood to include roughly what is ours by "natural right": i.e., what belongs to persons in a state of nature. That state, though hypothetical, nevertheless takes on in the imagination a weight as great as any ever granted to God's word or the authority of the church. Nature itself becomes a text; the words "printed" there, the facts of life, are taken to be the justification for action and rebellion, just as the Bible's words were understood, before, to be the basis for defending the existing social order. Both the American and French revolutions were legitimized in theory by ideas of natural law, natural right, and the human condition in the state of nature--all of which were understood to provide a factual underpinning for a vision of freedom, since freedom was merely the extension, into the social realm, of what had belonged to persons in a previous state.

The first wave of revolution, then, put men and women back into nature, and it replaced God with nature as the main point of reference for theories about society or the state. But the nature involved was in many ways nothing more than a useful fiction. It was a projection onto the past of what would have been, thrown forward, a kind of science fiction or utopia. Reading Locke, Hobbes, or Rousseau, for instance, one is struck by the vague arbitrariness of their images of the past; science is not yet present. Or, rather, one might say that both nature and the past now occupy the center of thought, but science, as applied to them, is still peripheral, has not become central, has not lent itself to

vision. What we see is the philosophic *use* of nature. One can feel at work in it, at times, the immense impact on mind and heart of the discovery of the New World, and the changing images thereby created of what our nature was. But even that is used hypothetically, tentatively, is almost *painted* onto the past to create a backdrop, a framework and a theoretical foundation for political action.

But that, of course, is only the beginning of the process. It crests again in the mid-nineteenth century, when the natural world--previously a postulate, a semi-fiction--is established in fact and transformed again in the imagination. Anthropology, archeology, biology, geology--these "earthly" sciences become, taken together, a re-creation of the physical world. It is something of a new neolithic age. Human attention is fully turned again to the physical world. It is a far cry from the crude, large-thighed figurines which marked the art of the neolithic age to Lyell's geological discoveries, but there is something common to them both: a focus on locality, specificity, and the foreground of perception--the earth itself and its awesome presence. One can feel in it the return of the local gods who had once inhabited rocks and trees before disappearing with the rise of priesthoods and "official" religions. Darwin's attention to flora and fauna, Lyell's observations of soil and stone--these are akin to the patient generations of observation and experimentation through which men and women long ago discovered what could be eaten, how it should be grown, what had to be done to domesticate it. Here too, as in those days, the world of nature is made into a human world. It is--make no mistake about it--an act of love. Just as the neolithic farmers sometimes lay full-length upon their fields to seed them with their own bodies, others now extend them into the natural world, *penetrate* it, thereby (as we shall see

later) allowing it to enter them, becoming a part of themselves.

It is at this point that biology in general, and Darwin in particular, become central. Not only man "in nature," but *the nature of man*, becomes the dominant question. The shift is a huge one, and irrevocable. Nature passes through and into us--as if invited by the attention paid to it. With Darwin we take on, inside, a dimensionality and eventfulness which had previously been seen as external to us, occurring around and *to* us. The temporality and depth which had previously created a past for the world itself now creates in us a similar depth, a similar set of shadows. What Darwin accomplished was not, as it sometimes seemed, a reduction of humanity. It was, on the contrary, a deepening, a partial redemption, for from his time onward men could feel, in themselves and *as* themselves, gravid and ongoing currents of change.

Of course what we have of Darwin in our popular mythologies is only a fragment of his work or thought. Animal aggressiveness, "the survival of the fittest," nature as eternal struggle--these are the simplistic notions we have made of his work, filtered as it is through what the English made of it, using it to rationalize their empire and colonial policies. In actuality there is as much in Darwin about the cooperativeness of species (what Kropotkin called "mutual aid") as there is about aggressiveness. In *The Expressions of Emotion in Animals and Man*, for instance, he stresses the cumulative generational effects of learning and choice as much as he does the effects of genetic mutation. Evolution was not, for Darwin, a mechanical or mindless process; it was, on the contrary, participatory, cumulative and volitional: the interpenetration of nature and mind. The "state of nature," which had been, for Rousseau, a static condition, had become something else altogether. It was

eternally present *within* persons, even in the midst of society, and it was present as a state of flux, a series of events occurring beneath consciousness but somehow subject to learning, experience and choice.

It is precisely that kind of perception, along with others borrowed from anthropology, biology and other emergent sciences, that one sees at work in Marx, Engels and other nineteenth century political theorists. One is struck in their work by the fact that they make as much use of anthropology, biology and ethology as they do of political or philosophic theory. Their visions of a social future are constructed to be both extensions of the human past and of human nature, and their work is a reintegration of science and philosophy--all of it in the name of liberation. Just as Darwin restores nature to men and women, Marx restores history to them placing them at its center and redeeming the past struggles of others for survival and freedom. History is no longer perceived as an inevitable tendency or direction; it is understood, instead, as an arena for action, *a field of creation,* which is how Darwin perceived evolution. In that process the centrality of human choice and the uses of collective action are added to our range of perceived experience; a crucial aspect of human nature, the natural tendency toward solidarity, is made a part of what we feel to be ourselves.

What is most striking about the nineteenth century is precisely what is so strikingly missing from our own age: theories about cooperative action, community, and the human appetite for political, social and moral lives. Socialists, anarchists, communists--all took for granted, in themselves and others, a capacity for reason and a desire for freedom and justice. They assumed those to be the natural tending of intelligence, as strong a need in persons as any other kind of desire. In part, that belief was founded on

what had recently been discovered about the human past. The range of imaginable futures was increased immeasurably as people came to understand the plasticity of their own nature. Though we in America tend to see the past and evolution as proof of the inescapable mechanisms and "programming" of nature, that was not how the same material was understood in the nineteenth century. Then (as is sometimes true of some Russian psychologists now) the variety of human experience, the multiplicity of social forms, the passage from one social condition to the next, were all taken as proof of the uses and possibilities of solidarity, desire, choice and will. They were the source of an immense hope that moved large numbers of persons to action when combined with the needs they felt.

Perhaps the loveliest single text produced in the period was Kropotkin's *Mutual Aid.* It is there one can find biology and history combined to create a gentle but visionary politics that is articulated into concrete suggestions for social and economic organization. Kropotkin's belief in human possibility is based on the natural capacity for cooperative activity that he finds in both the animal and human realms. Our "animal" nature is for Kropotkin (as it later was for Wilhelm Reich) not at odds with our reason or our need for community, but its *source*: a kind of perpetual and innocent desire which manifests itself again and again in self-determining and cooperative social forms. What Kropotkin offers is a kind of loving attitude founded on fact, something that is closer in a way to Tolstoy than to Marx. Yet where Tolstoy finally based his anarchism on the gospels and the word of God, Kropotkin bases his on human nature, on what might be called a natural "appetence for good," and his belief in that is founded not only on his own research, but on the same evidence in Darwin's that the English made into the idea of

the survival of the fittest. For Kropotkin, as for most of his radical European contemporaries, science and the new view of human nature created a new hope, legitimized a new kind of revolution, revealed a human need for new kinds of political action and organization--all of which had to be appropriate to newly emergent (because newly imagined and understood) human needs.

I stress that sense of newness and emergence here, as I did in talking about the Enlightenment and earlier revolutions, because it is precisely that evolutionary aspect of self-creation, and its relation to revolution, that makes Ray Peat's work significant. In some ways our own view of nature and ourselves is beginning to crest in the same way that it did in the eighteenth and nineteenth centuries. In the scientific world and in our own imaginations different views and images vie for the central position in how we think, and in many ways the future of both thought and politics depend on which ones are triumphant. Each of us, though largely unaware of it, is even now becoming other than we were--but only as *potentiality*, in a raw and unfocused way that is going to demand from us, *already* demands from us, some kind of willed thought and action to give it a generous and human shape.

The sources of that third phase of our view of nature can be found, at least in part, in both Freud and Pavlov. At least that part of it begins in them which deals with the nature of individual identity: the way the flow of life is experienced *in the individual* as a ground of being, a drama of the species localized as self. For Darwin, Marx and their contemporaries it was the species in general which was understood to play the central role in nature and history. For Marx the idea of *classes* is borrowed in part from biology, and it represents a kind of sub-species rather than a group of varied, individualized persons. There was nothing

wrong with that; clearly it was a step forward from the kind of thought to be found in Hegel: the idea of human nature as subservient to a general "spirit," and the identification of culture with the state. In that sense, Marx's work is a step toward individuation; history is seen as a common labor, is made human. But for all of that, with Marx, as with Darwin, the individual remains a construct, something of a metaphor, an integer, a useful way of talking about the larger group.*

It is only in the late nineteenth century, with Freud's work in psychoanalysis and Pavlov's in psychology, that the depth of nature is taken to be dramatically present in each creature. In both cases nature is deeply internalized, is seen to exist at the very center of mental or cellular life. But at the same time something dangerous begins to happen. The idea of self is isolated from the world which ordinarily surrounds it. Psychoanalysis and psychology grow away from philosophy and politics. The inward focus of attention leaves the larger world apparently unacknowledged, and that is unfortunate, for the isolation belies the implication of their thought. For Freud, both nature and history, as id and super-ego, are placed at the heart of individuality and individuation. They are understood to be eternally present ("eternal Eros," writes Freud) as ongoing processes: a set of dynamic relations determining the development of each psyche. Each psyche, in fact, is perceived as the potentially intelligent and volitional mediation between nature and history, id and super-ego. The ego itself is a communal work of self-creation, is the stuff of nature turned to human

*It is for that reason, perhaps, that communist and socialist theory, as opposed to anarchist theory, has never really produced a viable concept of individual liberty, though they do have theories of *freedom*, a more general idea.

use: not an alternative to nature, not something held against it, but the *form* given to it, the shapes we allow it to take. The person is one of the arenas in which the great confrontations, struggles and reconciliations of each age occur; we are not merely "in" history or culture, but these comprise the life of the mind and tissue, since that life--at all its levels, in its various chambers and extensions--is also the presence, in us, of the historical world. Consciousness is a product of that world, just as the sub-conscious is the internal existence of a world of nature as real and as gravid as the world of animals and plants.

It is easy for Freud's followers to pick and choose among his various ideas and emerge, as we do in this country, with what amounts to a new form of solipsism or mechanism, a view of the life of the psyche as autonomic, essentially mindless--a clockwork destiny akin to the way history or evolution are sometimes seen. But those who do that merely add their own poorly understood biases and class-blindness to those already at work in Freud himself, and the result is that we make of Freud's work what the English made of Darwin. Though Freud's great dream of ego and reason was that they would be put to the service of Eros and take us toward the future, we reduce his ideas to trivial notions of adjustment, sublimations, repression, etc. We eliminate the visionary and implicitly moral aspects of the work, forget its speculative beauty and the generosity of its hope, and the end result is a theory of the self in which the self is understood only in isolation from, *not in relation to,* the world around it. What Freud did for convenience (isolating the self for study, to see it clear) we continue to do out of our cultural bias. Having forgotten the existence of organic community, wishing to deny the full weight of history, reared to accept institutional roles instead of deeply felt relation, we see in the individual self nothing more nor

less than the distorted mirror-image of bourgeois and mercantile individualism--not the self in the splendor of its human appetence for others, but a self "cast down" and in perpetual humiliation. Our psychology and therapies reflect the alienation at work in our social and economic systems, and we use them to screen out from consciousness whatever would call those systems deeply into question.

The same thing is true in some ways of Pavlov's work. In this instance I am less sure of my ground than I am in Freud's case. I know Pavlov's work less well, and I rely here on what Ray writes rather than my own conclusions. But nevertheless it seems clear that if one comes to Pavlov's work with a belief in the uses of freedom, and a sense of holism, and can also set aside what Watson made of Pavlov's work, then one can find in it some of the raw stuff which must be woven into a vision of human complexity. What happened to Pavlov's work was similar to what happened to Freud and Darwin. Its implications were developed by later researchers mainly in one direction, toward mechanism or mindlessness, though it *is* true of Pavlov, as it is of Freud, that those implications can in fact be found in the work. But there are other and more compelling elements which can also be found in it. What interests me about Pavlov is the way in which the force of nature is seen at work both in the organism as a whole and in the individual cell, and in which these seem simultaneously present in one another. Nature is miniaturized, and it materializes at the very core of being, in its smallest parts. It opens, inwardly, into an internal universe as extensive as the macrocosmic, external one, so that we seem to grow in size. What Freud restored to the mind, Pavlov restored to tissue. It is there too that mystery resides and vision can be found, and that is a source of power.

Do I make myself clear? What I am saying is that there is already enough information, theory, image, evidence and hard speculative work for us to begin to deepen, in a clear and visionary way, the ways we see our own nature and our place in nature. It is both necessary *and* possible at this point in time to add to the impetus and lessons of previous revolutions what we see that others did not. It is not that those ways of seeing were insufficient then. Clearly some visionary dreams, values and ends do not change. Fraternity, equality and liberty; Kant's "kingdom of ends"' Rousseau's notion of the general will; Kropotkin's mutual aid; Proudhon's ideas about justice; the recurrent human dream of cooperation, social justice and the equal distribution of wealth and access to power--all of this can be taken as a kind of cumulative human wisdom: not to be discarded, but to be deepened and extended anew in terms of how we now see ourselves. It is, for us, the *act* of deepening and extending which is crucial, because it is there, in the felt enlargement of vision, in the thrust and excitement of the shape the world takes as image and desire, that one finds at least part of the courage it takes to act in the world.

The partial answers our science offers have raised a new set of crucial questions. Can we learn to talk about freedom, morality, society, ethics and choice in a way that includes and illuminates what goes on in the nervous system itself, in the individual cell? Can we talk about what goes on in the cell in a way that revivifies our belief in freedom? Can one see the eventfulness of the microcosmic world as more than a form of inevitability? Can one envision it in a way that restores to it a teleologic identity, one effected and partially expressed by the larger systems we build through vision and reason around us? In what way are those miniaturized and yet gigantic operations a part of vision and

reason? Are they changed by it? Are they its partial source? What is their relation to energy and desire? Do they produce them? Express them? In what way do they respond to changes in consciousness? What is their role in imagination? How are they changed by imagination?

These questions are close to the heart of what Ray is getting at here. I do not myself believe that such questions or their answers can supply us with the necessary moral or political grounding without which our theories lead us always askew. But if they are not included in our moral and political concerns and woven into our vision, then we are left with something far too narrow, too unconvincing to be of use. The questions raised here give to that vision a substantiality it otherwise lacks. They demand, implicitly, that our social actions and systems honor the full extent of our self-knowledge. When Mao, for instance, talked about the "cell" as a principle of political form, he was referring to the ways cells operate in nature, and to their relationship to the larger organism whose parts they are. But what happens as we understand the cell in different biological ways, as it becomes more ambiguous, a bundle of energies rather than an identifiable *thing*, an event rather than a place? How does that change--in the long run, in deep images--the ways we will eventually see ourselves when grouped together? That, in part, is what I mean. The sciences are a challenge, a goad. We cannot simplify things by turning away from them, for they are there always--*the presence in thought of the physical world*--demanding, as they provide us with theory and information, that our vision account for the full depth of experience. They make impossible for us simplistic or reductionistic solutions or approaches.

That is not to say there is not, implicit in science, in its language itself, a kind of reductionism--or, at least, the

permanent danger of reductionism. That is there, of course. One can find it in Freud. One can find it in Pavlov. And one can find it even more in those who come later and make use of their theories. It is difficult, even with the best of wills, to keep in mind the full field of human significance in which discoveries, facts and theories have their lives. It is easy to forget that each one of them occurs in a moral, political and historical realm, that each one is a part of, and an act upon, a field of significance defined by both the imagination and heart and larger than what we have learned scientifically. The significance of moral and historical concerns is not necessarily generated by science itself; they must be brought to it by volition and will, by a felt love of the world, a sense of human freedom and justice. If those elements are not present as we do our investigating, *before* we do our investigating, what we learn through our sciences will be exploitive by its very nature. Fortunately, Ray Peat understands that--I do not mean to suggest he does not. The science he offers us here is offered as what must be woven into vision, wedded to both politics and poetry before it is whole. Science is perceived not as a way of defining reality; it is, instead, a way of perceiving the full extent of the reality that must be defined and re-envisioned and then *made* real--through action in and upon the world.

That, I think, is a crucial point: the necessity of action. Perception is not sufficient in itself. In fact, if it does not impel us to action then something is wrong with either the perception or the way we receive it. We like to think of the future in terms of inevitability, apocalypse: in inescapable slant to destiny. But that is not the case. The world does not move inevitably toward light or darkness--not in any particular culture or place. It oscillates between them, and each historical epoch or moment is a balance between them established by specific human

choices: the collective decisions people make or fail to make, the kinds of responsibility they take upon themselves. Vision does not simply visit us from the Gods. It is a cooperative, creative work which is ours *by nature:* the impulse in flesh itself (Freud called it Eros) toward the world, our appetite for entering and changing it--a form of love.

At the moment, of course, we have trouble keeping that in mind. We seem befuddled in America by both politics and history, exhausted by them, propelled by shame and fear into a bourgeois dream about the end of history, or its existence outside of use, apart from human work. But we will not be saved by any magic external to ourselves. Either we learn to act within history in accord with our deepest vision or we disappear from it altogether. Ray Peat knows that, and what he offers us here is a bit of the beginning of that *laborious* process. Ezra Pound once said that all good literature was "an impulse to action." And Rilke, describing an archaic torso of Apollo, said of it: "There is no place that does not see you. You must change your life." There is a point at which science, given shape by the constraints of evidence and demonstration, comes to the same visionary condition: impulse to action, injunction to change. It does that through the creation of deep images which generated energy and organize desire, moving us--as does all energy and desire--to reach toward the world, enter and change it. It is not a process many of us trust at the moment, we do not ordinarily think of science as a complement to politics in the struggle toward freedom. But Ray Peat manages to convince me that it is. I feel in many ways emboldened and heartened by what he describes here, and less lonely. I can see in the hard work of others much of what I know intuitively, poetically, to be true, and there is in that a freshening of hope. There is something here to

lay one's hands on, something to try to wrestle into form, to put to use in the world. Ray likes to talk about Blake, who in turn believed in *Jerusalem,* the just and joyous city to be built not in heaven, but on "England's green fields." Jerusalem is the outward shape of the collective nature of our inner lives, something we share even in our fragmented condition, but which will become whole and clear only when we have managed to "build Jerusalem" in the actual world.

That is the work Ray has in mind in *Mind and Tissue:* the *real*-ization of vision--the making real of what exists now as image or desire. He understands that vision is a collective act, a communal work: not the romantic solitary hero working alone to save the world, but a community of persons moved by a vision shared among them and theirs by nature, by virtue of their humanity. Each of our disciplines or crafts is an extension of something larger, the limb of a visionary body which exists in entirety in imagination and toward which we move, *becoming,* as we act in the world. The difficult task we confront in the world is maintaining, in our apparently separate spheres, a sense of the wholeness which moves us and toward which we move. Ray understands that wholeness, and it is that understanding which generates in this book, at the same time, a sense of power and a sense of humility. The scientific truths Ray talks about are perceived in a field of significance which is in part produced by science but which is also brought to it from other realms: politics, history, morality and philosophy. In that sense, though he would probably blanch at the notion, Ray seems to me something of a Kantian. He accepts the nature of persons and their well-being as a "kingdom of ends"--not in the sense that they are finished or complete, but that they are irreducible *goods* against which all action and theory must be judged. The shadow of life in all its complexity falls across each scientific fact or theory, is

a standard against which it is measured. For Ray science is simply one of the gates which open into the world, and it leads us into chambers where we meet others who have arrived there in different ways. It is part of--I was going to say the "restoration" of being. But that is wrong. It is part of the *creation* of being--the task handed us by existence itself. To hold in the mind, at the same moment, the energetic event that is the cell, the processes that form the stars, the human nature of freedom and desire, and to feel it all as *ourselves*--that is the world's gift to us, one spelled out at times by our sciences. It ought to lift us like a tide, propelling us, as sometimes it does, into the world, where our task is, always, to make a proper home for it and ourselves.

PREFACE

In the two years since 1973 when I wrote Mind and Tissue, one of the few good trends I think I have noticed in the US is an increasing distrust of empty formulations, ritual, and authoritarian professionalism. People are possibly more often looking for something that works, rather than just anything that sounds good. In this context, a book about Soviet brain study should be useful to a broad section of the population, since the Russians have for many years been using techniques of "hard science" for the achievement of goals which in the US have fairly recently come to be identified with Humanistic Psychology. Besides introducing readers to some useful approaches and techniques in psychology, I think the book can provide a new perspective on science itself, showing how it can be humanistic and life promoting, rather than just "ethically neutral."

To the extent that I claim science to be a humanism (as Sartre says that socialism is a humanism), I find myself being viewed as a non-scientist by American scientists; when I claim that broadened perspectives would be liberating for science students, I find that American scientists retreat in horror. Humanists who find those attitudes of scientists repugnant also assume that one should conclude that science itself is at fault. I intend this book to be a defense of science (as science might be), and a demonstration that science is properly humanistic, that no perspective should be shut off arbitrarily, that scholarship should be acceptable to scientists.

If the Cold War in science is to end, I think we must achieve clarity and self-consciousness by impugning the

scientists who have built their careers on loyalty oaths and silence in the face of McCarthyism or other forms of censorship, mind-control, or fascism. We should remember that hundreds of German scientists who condoned "racial hygiene" and murder-experiments are still contributing to the atmosphere of the scientific community.

The concept of science's "ethical neutrality" is largely an outgrowth of Hiroshima and the German Science-Murders. The American doctrine of "eugenics" was renamed "human genetics" after the embarrassment of the Holocaust, but the essential doctrine has lived on in the academic world. "Ethical neutrality" has been used to confine guilt to individuals. (And it is even more refined than that: The man who devised the genetic rationale for the Holocaust can be honored by distinguishing his political intention from the abstract content of his work; even guilty individuals aren't really guilty in the ethically neutral world of science.) But there are systematic motivations of a cultural and historical nature which shape the nature of science. The distortions and falsifications of the pharmaceutical industry and the nuclear power industry have seriously degraded our scientific culture in recent years. These pressures are not likely to decrease in the near future.

If American humanistic psychology, the tradition of people like Kurt Goldstein, Carl Rogers, and Abraham Maslow, can assimilate Soviet brain science, I think it can complete its displacement of the old dogmatisms in American psychology and physiology, and will then be in a better position to make a deep and lasting contribution to the culture itself.

Chapter 1

(Historical origins of Russian brain theory)

In the Spirit of Matter

A culture is a theory of human nature. Some cultures are self-deprecating, others are split in their image of a noble class ruling an inferior class. One of the themes of Russian culture has been that of a potential waiting to be fulfilled--Russia waiting to lead the world to spiritual awakening, the spiritual richness of the peasants, etc. In the 19th century, Khomyakov and Kireyevsky contrasted Russia's "community" to Europe's spirit of violence, competition, and conflict between races and classes. They believed Europe was the product of Roman and Germanic conquests, and was deformed by authoritarian and rationalistic Catholicism and self-centered Protestantism. Oriental influences have contributed to the complexity of "Russian" culture, but we can get a valid insight into the culture just by briefly considering how their Orthodox Christianity differed from our western Roman Catholicism and Protestantism.

According to M. Spinka, "The eastern theology had its roots in Greek philosophy, while a great deal of western theology was based on Roman law." Typical differences were the Romans' emphasis on the divinity of Christ, their enforcement of clerical celibacy, and the limitation of the right of confirmation to the bishop. A deeper difference is the absence in the Eastern Church of creeds as summaries of what must be believed. The distinction between Greek philosophy and Roman law is the distinction between knowledge and power.

Still, the Roman church has been deeply influenced by Aristotle, through St. Thomas. The Arabic translations of Aristotle first came to the West as distorted Latin translations, but Thomas got his Aristotle directly from Constantinople, where his philosophy had been studied since the time of Justinian.

Protestantism has followed Luther in hating "Aristotelianism." Thus, we can see a "gradient of Aristotelianism" rising toward the East, within Christianity.

There is a well known theory that the Protestant form of Christianity (especially Calvinism) is the appropriate ideology for capitalism, as Catholicism is the ideology of feudalism. The preference of Protestants for Platonism can be interpreted in relation to the historical need for a more absolute kind of idealism. Anyway, the important point for understanding some of the present cultural differences between Russia and the West is that Russia has for centuries felt the influence of Aristotle, and has not suffered from the influence of Plato or Calvin.

We still hear people making disparaging remarks about "Aristotle," but what they are really disparaging is the formal logic of medieval Christianity, which had learned nothing from Aristotle except his logic, and made poor use of that.

Many of the themes of Western philosophy, such as the analysis of "substance," can be traced to Aristotle, as others can be traced to Plato, but the remarkable thing is that Aristotle's common sense and extensive knowledge of nature were lost in the process of "refinement." Aristotle was a real scientist, who gathered data and gave meaning to them by finding general theories to explain them. The ideas of growth and change were important to him; Engels described him as a dialectical thinker, with "fluid categories," just the opposite of what most people mean

when they say "Aristotelian." For Aristotle, growth and evolution are both a process of realizing the thing's nature, which was already present as a potential at the beginning of development. Engels and Marx seem to have vacillated on this question of teleology, of an inherent purpose in matter. This is a scientific question as well as a philosophical problem, and is now being increasingly discussed by biologists and chemists (e.g., Rohlfing and Oparin, in *Molecular Evolution*, 1972).

This evolutionary question is of great importance for brain study, but unfortunately it is seldom discussed in these terms in the Soviet scientific literature. In fact, inheritance of differences in mental ability is usually denied, so that all effort will be used to improve the environment, instead of justifying deficiency as "inherited and therefore fixed." Also, the conflict between Mendelist geneticists in the big universities (Moscow and Leningrad) and the Burbank-Lysenko followers in the agriculture research institutes still exists, despite the fact that the government no longer gives its support to Lysenko's doctrine, and this may contribute to the problem of studying brain evolution. Of course Marx's and Engel's theory of labor as the main force in creating the human brain is often discussed in the Soviet Union, as it is in the United States since being popularized by Jerome Bruner.

Since Christians used the idea of purpose or teleology to deny materialistic explanations of evolution, most materialists have been extremely careful to keep anything resembling a "vital impulse" or a teleological force out of their theories of development and evolution.. If time, history, and dialectical development are to be affirmed, they have felt, any tendency of matter to favor a certain line of development must be denied, because it would let preformationism and dualism get a foot in the door.

How much weight should be given to matter, and how much to the situation in which the material exists during a certain time? An image illustrates two extremes: imagine finding an old cat-gut violin string that has been coiled in its package--stretch it out beside a silver watch-chain, coat both of them with a little sticky pitch, and then form each of them into a variety of geometrical shapes; with the cat-gut, some shapes will be impossible, but it will almost spontaneously return to its coiled shape. With the watch-chain, all shapes will be about equally easy or difficult. Is matter as passive as the watch-chain, taking one form as easily as another, and being limited only by circumstances, lacking intrinsic preferences? Aristotle held that matter was not passive in this sense, that given the necessary conditions of life it realizes its potential, and takes its form neither from the environment nor from chance variation. Naegeli's orthogenesis and Osborn's aristogenesis are modern forms of this idea--the most recent expression is in *Biochemical Predestination* by Kenyon and Steinman. Another kind of theory also excludes pure chance, but gives environment a role in forming the organism: Eimer held that orthogenesis (straight-line evolution) could result from a molding influence of the environment, and Lamarck emphasized an active (physiological) adaptation of the organism to its environment. Darwin would fall into this group to the extent that he denied that variation was random, and also to the extent that he believed that natural selection was not the only mechanism of evolution.

Ironically, the neo-Mendelists have almost excluded matter and its properties from their genetic theory of evolution, though many of them feel that they must do so to save their "mechanistic" science from the "creationists" who oppose even the idea of evolution. Random variation of the genetic material is their basic assumption, and natural

selection of certain alterations is their proposed mechanism. Both of these doctrines, randomness and natural selection, are important ideological components of capitalist culture, so the ethno-centrism of the neo-Mendelists is just a little more modern than that of the creationists who threaten them.

Oparin and his followers (and there are growing numbers of them in the United States) have demonstrated that many chemical reactions and structural processes which closely resemble those in organisms can occur spontaneously under conditions existing on earth, as a result of ordinary chemical reactions without having to invoke random variation or natural selection. Pauling and Zuckerkandl (in *Molecular Evolution*) have convincingly argued that the doctrine of "inherent randomness" is really a doctrine of the mind's inherent inability to understand matter--an ideology of subjectivism posing as a scientific attitude.

To find more convincing general mechanisms isn't to deny that chance variation and even Malthusian selection sometimes occur. Also, endless flexibility and potential for new growth is not denied by holding that there is a "tendency" inherent in matter, since the "tendency" would also be modified (and maybe intensified) in more complex structures. (Later, we will consider how physical resonance might constitute such a tendency of matter.)

Whatever influences other than Aristotelian Christianity were acting, Russian culture in the 19th century was probably the richest and most spectacular in the world at the time, with great achievements in many areas of science, literature, and music. (Though England's literature, France's painting and sculpture, and German physics were high points of the 19th century; my point is that Russia had several great traditions. Russia's weakness in the visual arts

is notable; Salvador Dali suggested that their eyes were damaged by too much snow.) It was a culture that was ready to accept the Romantic historicism of Marxist philosophy, even though the economy wasn't advanced enough to be ready for a real Marxian revolution. (Similarly, the Taoist dialectical tradition in China seems to have been favorable to Marxism, in spite of the primitive technology. Mao has been aware of this cultural factor which has made communization possible without the sort of great dictatorship of the bureaucrats, that the Soviets inherited from the Czars.)

Dostoyevski was an important thinker, whose novels investigated both psychological and social questions with originality. He advocated social reform and democracy, and believed that the highest spiritual values existed in the Russian peasants, with the result that he adopted Christianity with the attitude that if Russians believe it he should believe it. This attitude seems silly on the surface, but as understood by Dostoyevski it represented one of the highest human functions. A very good analysis of these ideas and discoveries has been made by A. A. Ukhtomskii, a major brain physiologist who studied Dostoyevski's books for guidance even in scientific matters:

> Long ago, since I was 19 or 20, I began to wonder wherin lay the essence of the problem that tormented Dostoyevsky. And it seems to me that that gradually became clear. You know, the hardest thing in the world for a person may be to free himself of his double, his automatic tendency to see himself, his faults, his shortcomings, his secret deviance in everyone he meets.... And only from the moment when the double is overcome is the road open to free communication with another!

> It is then for the first time that mind, heart, and word are revealed, making it possible truly to hear what it is that makes the person one has encountered tick.... An open heart and open and intelligent hearing detect and understand in the other that which the individual had been unaware of in himself, and which merely dully exhausted and tormented him from some undiscovered part of his insides! ...thousands...come from all directions to enter into communication with this person who had taught himself to see and hear the people who took the place of his discarded double.

In a more general comment on the story "The Double" Ukhtomskii wrote:

> In the final analysis this is a philosophical and psychiatric treatise about solipsism and self-assertion as the basic characteristics of a typical representative of European civilization....
>
> Dostoyevski wants to emphasize that the most insignificant, ungifted, little European-type person bears the embryo of "delusions of grandeur" because he has been seized by the "epidemic of self-affirmation" with a fateful incapacity to see in his neighbor an existence in the world equal in value to his own."
>
> My...task is to understand how the kind of sensitivity possessed by the *Elder Zosima* comes into being. I learned that it is created by a great physical effort, a tradition handed down from others, and an attitude toward the world

as toward a beloved, respected companion with whom one is close to the point of intimacy.

...an individual cultivated in this way turns out to be uncommonly sensitive and responsive to the lives of other persons and is able to readily place himself in the position of the other, with *his* attitudes and tribulations.

Only if another person is moved and extends patient help, can an individual be torn out of this *fateful subject-object relationship,* owing to the fact that the world is to each individual what he deserves, and the individual is like his particular world! For one needs *nothing more nor less than to change in a person his physiological perception, that which is physiologically customary, the continuity of his life....*

Whatever an individual's dominants, such too is his integral image of the world; and whatever his integral image of the world--whatever his behavior--such is his happiness and misfortune--which is the fact others see. It would seem that one can say that the *elder Zosima* and those like him possess a technique for penetrating into the immediate future in a highly unusual way and with regard to the single individual closest to them. They possess a *dominant for the personalities of others....*

As soon as one senses the fundamental superiority of living reality and persons over self-asserting, self-isolating knowledge seeking security for itself, one discovers that it is only via culture in the whole man, the culture in his deeds (will and love) that a *vision* can be

"highest" part of the brain, the cerebral cortex, participated in the "simplest" seeming reflex. The English physiologist, Sherrington, also recognized this, and said that the old ideas of isolated reflexes were simply fictions. For Pavlov (and Sherrington) the whole organism had to be the subject of study. Somehow, Watson argued for the study of the parts, and seems even to have denied the existence of such a thing as an organism! Apparently this would have brought him too close to consciousness, since presumably it is the organism which is conscious. Modern American Behaviorism (including Skinner) is still close to Watson's position, and generally ignores Pavlov's real work. One small advance in Skinner's work over Watson's is the recognition that pain and the avoidance of pain are not the only motives for behavior.

Skinner's environmentalism is sometimes viewed as a humanistic aspect of his theory--and increasingly so. Carl Rogers has recently remarked that Behaviorism is a valuable complement to other therapeutic techniques. However, Skinner still holds a strongly genetic, rather than really developmental view of human abilities. A common American idea of the brain is that it is "genetically" "wired up," and some degree of rigidity is assumed even by the environmentalists, but beyond the rigid inherited system, there is assumed to be a passive ability to learn.

In Russian brain physiology, increasing specialization of function in certain areas of the brain is considered to be a feature of evolution, but plasticity is believed to be the outstanding property of nervous tissue, especially of the cerebral cortex. An American (Pietsch) has demonstrated that frog and salamander brains will work normally even when removed and put back in backwards, but this fact hasn't impressed many of his American colleagues. In Russia, such demonstrations of the extreme

plasticity of the cortex are central to their thinking about the brain. For example, the leg nerve and the vagus (digestive) nerve of a dog can be "criss-cross" stitched, and the dog will recover his normal walking ability. However, if his cerebral cortex is later removed, the altered arrangement of the nerves will no longer be compensated for by the cortex, and the dog's leg will not be able to function normally. The adaptation is obviously "teleological"--the dog achieves its purpose of walking, in spite of the rearranged nerves. The cerebral cortex is thus an "organ of purpose."

It has long been known that when part of the cerebral cortex is destroyed by disease or accident, the function that was "localized" in the lost portion can be regained. All functions, however, will be slightly diminished by the loss of that formerly "specialized" tissue. (Even body functions such as aging appear to be affected by the brain loss.) This capacity of the brain to restructure itself is believed to be based on a plasticity in the nature of the nerve cell itself. This is another major point distinguishing Soviet and American brain physiology, since the tendency in the United states is to see the nerve cell as a simple on-off switch, regulated almost exclusively by external, "synaptic" influences, of excitation or inhibition. Since radical plasticity is only a minority view in the United States, there isn't much need to explain how "restructuring" can be achieved. When it is attempted, as in Pribram's hologram theory, the synapse, and processes of interference occurring at the synapse, are still the basis for the explanation. Probably the underlying reason for the conservative thinking is the view that the nerve cell is an ionic solution separated from its environment by a membrane, internally "simple" or randomized as far as its signal function is concerned, and capable of interacting only by means of special points on its surface, the synapses. This ignores various features such as

radial and longitudinal gradients of electrical potential within a single cell, or metabolic and structural conditions which lead to complex states and processes and interactions which might serve to handle information more effectively than "switches" could.

In Russia, a different view of cell structure is held by the majority, and this view is one which allows for more complex interactions of cells, and makes possible a more direct experimental approach to the study of inhibition, fatigue, excitation, etc. For example, a given stimulation can be excitatory or inhibitory, depending on the functional state of the nerve cells; a given substance can be either excitatory or inhibitory, depending on its concentration; the physical state of cell proteins can be used to determine the state of the cell, as can stainability of the cells. Nevertheless, Pribram's version of the hologram theory of brain function was well received when he presented it at a conference in Russia recently--the basic idea in the hologram model, viz., diffuse storage, was already developed in Pavlov's analysis of each "sensory analysor" system into a nucleus and a peripheral section, and also in the idea of "latent reserves," both of which emphasize the diffuse interconnection of fibers from different systems. For Pavlov, though, the "functional state" of the nerve was more interesting than the synaptic events.

Aristotelian assumptions about the "tendency" of matter to develop will result in a kind of "environmentalism" which is very different from Skinner's. For example, "self-actualization" has meaning only when the concept of "organism" is open, developmental, and in a "dialectical" relationship with the environment, but with some intention or direction inherent in itself. On the social level, Skinner's theories would make smooth-running the main virtue, instead of moving toward higher levels of being.

Orientation toward the future is more important than "homeostasis" for Soviet brain theorists, and is an attitude that derives from Aristotelian philosophy as well as from Marxism. For example, consider the ideas of pleasure--for Aristotle, it was the result of the free, unimpeded flow of a desired activity, but for the strongly anti-teleological theorists in the West, it is the *cause* of desire, by way of learning, instead of its result. If sexual pleasure were the cause of sexual desire, wouldn't adolescents in a sexually repressive society have an easier time than they do? Rather than mystifying and denying our experiences it would seem more profitable to study and try to explain such clearly purposive, "teleological" processes as sexual desire and sexual behavior. An inborn desire is a valid subject for scientific study. The philosophical bias against the study of desire, which dominates western thinking, is a peculiar new form of mysticism, which tries to explain everything in terms of the past.

A Western tradition, phenomenology, associated mainly with Vienna, has also made good use of Aristotle's knowledge: Brentano and Husserl used the concept of "intentionality" to explain perception and knowledge. Kurt Goldstein's organismic studies of the nervous system were influential in the development of the phenomenological views of Carl Rogers, Merleau-Ponty, and Abraham Maslow (best known for his popularization of Goldstein's "self-actualization" idea). Because of the Aristotelian content, phenomenology is most widely accepted in Latin countries, especially France and Latin America.

Ukhtomskii's idea of the "dominant" shouldn't be interpreted as "just an earlier form of Gestalt psychology," which of course is one of the forms of phenomenology. Some forms of Gestalt theory are practically identical to Ukhtomskii's theory, in emphasizing the ability of the

organism to form new unities: Goldstein and Merleau-Ponty are in this group. But another school of Gestalt Psychology, and phenomenology, stays closer to Husserl and the neo-Kantians, in emphasizing *intrinsic* forms of knowing, as opposed to empirical forms. Symbol thinking and inborn limits to knowledge are doctrines of this school: These Gestalt subjectivists accept the theories of Cassirer, Chomsky, Piaget, and Monod/Stent, and are antithetical to the "Ukhtomskii school." It should also be pointed out that Carl Rogers' version of phenomenology denies objective conflicts of interest, and as a result is popular among United States business leaders: Rogers has argued, for example, that there is no real conflict between workers and owners, and that "good communication" will lead to resolution of conflicts, rather than to the understanding that wages and profits are really opposed. The fact of power is ignored. The theory of generality isn't typically a strong point of Gestalt psychology and phenomenology; their focus is on the here and now.

Even Marxism seems to have incorporated some of these insights into perception which were current in the 19th century. The Marxist idea of "reflection" of reality in the mind is both active and objective. Leontyev and Gippenreiter (in *Psychological Research in the USSR*, 1966), following Marx and Engels, describe mental processes "as a special form of activity which practically connects man with the world of objects that surround him." Another way of considering "reflection" is that every organism exists in interaction with its environment, so that a certain kind of environment is "assumed" by an organism at a certain stage of evolution: The environment in a sense is a completion of the organism's structure, since the organism can't exist in isolation, and is selectively sensitive to the appropriate aspects of its environment, such as food and

threat. We have evolved a complexity that allows us to "select" a complex kind of environment to which we respond, and our existence depends on the objective interactions between ourselves and our environment. Our consciousness is interaction. It is a condition for action, but it also is derived from our activity in the world. To say that it is "objective" in this way is not to deny the possibility of mistakes and perversions, but it is to claim that in *every* human idea, perception, or theory there is some truth, something worthwhile, if we are able to extract it.

*Quoted from V.L. Merkulov, "The influence of Dostoevsky on the creative work of A.A. Ukhtomskii," *Voprosy filosofii,* No. 11, 1971, *Soviet Studies in Philosophy*, Vol. XI, No.2, Fall 1972, p. 195.

CHAPTER 2
THE IMAGE

As Westerners, we are accustomed to a certain dryness or abstractness in scientific and academic matters. "Just reporting the plain facts" is taken as a kind of ideal, in the U.S. particularly. If we think about Soviet intellectual life at all, it is often to deplore the "politicizing" of matters that should be mere questions of fact. It is seldom that we can imagine a fact which is intrinsically "ideological."

A few western scientists have decried this "hard fact" syndrome in American and European science, but their criticisms are not really heard. In fact, these scientists usually criticize themselves right out of the world of practicing scientists, and into a kind of underworld that is populated mainly by older, individualistic intellectuals--Michael Polanyi and Albert Szent-Gyorgyi are the best known members of this scientific counter-culture which calls for intellectual wholeness, responsibility, and integrity.

For historical and cultural (and political) reasons, however, the Soviet scientist is likely to see everything he does as having social significance and ideological overtones, apart from any urging he might get from the bureaucrats to praise the insights of Lenin and Stalin into his particular field. Sometimes these paragraphs of praise that are included in occasional scientific papers seem simply bizarre to a westerner, who is used to politicians being politicians, and scientists being scientists. But the fact is that both Lenin and Stalin were remarkable intellectuals who believed it was their political responsibility to be very well informed about cultural and scientific matters. It is this same attitude which makes the Soviet scientist likely to choose problems with social significance, and to interpret his work in terms

of a large historical framework. While an American scientist undoubtedly does work within a definite intellectual framework, the framework is mostly tacit, and serves to justify the collection of "mere facts."

The whole analytical and skeptical tradition of British philosophy has not been taken very seriously by the Slavic and Latin* cultures, and Marxism has enabled the Russians further to disregard many of the formulations and proscriptions of Anglo-American thought. The idea of the *image* is the most important example of this dichotomy in the intellectual world, and is the crucial issue in brain research and all of its ramifications--including language, health, education, adaptation to new conditions, and the planning of work.

Since the image is taken to be real, and is such an obvious part of our ordinary existence, for the Soviet brain researcher the question is not *whether* images exist, but *how* they exist and what their relation is to sense, reflexes, learning, movement, and meaning. "Imageless thought" is typically dismissed[1] as a foreign mistake, along with Freudian concepts such as unconscious motivation.[2] American Behaviorists reject consideration of mental images as "mentalistic" and therefore unscientific, and many neo-Kantians or Cartesians--for example Noam Chomsky--prefer their mentalistic formulations to be composed of rules or other non-image units which are not directly accessible to consciousness. The most technical Soviet studies therefore often have a common sense, "man in the street" quality about them, and this probably accounts for some of the American disregard of them, since they seem to violate some of the "basic" (Western) scientific principles.

In the West, studies of the brain and behavior tend to focus on "motor," or efferent systems, since the essence

of their activity--i.e., movement--is objectively observable. A typical American formulation is that there are "motor programs" which govern behavior,[3] and that these are somehow coordinated with sensory, associative, or cognitive systems. In this theory, it is possible to put an electrode into the "motor region" of the brain, and to electrically activate a "motor program," so that, for example, a rooster with "emit" aggressive behavior. Soviet biologists tend to interpret this kind of experiment differently, because they view the sensory, or afferent systems, as being the most important aspect of the nervous system, and as constituting the essential organizing process of the brain. It has been emphasized[4] that most of the fibers extending from the central nervous system are sensory, and the cortex is thought of as an afferent system, after Pavlov.[5]

When we see the rooster "emitting" aggressive behavior, we should notice that his behavior is still co-ordinated, with reference to the ground, posture, and surroundings. If there were such a thing as a pure motor system, it would seem that we should be able to get the animal to "emit" a series of movements which would be independent of circumstances such as his initial position or posture. The "motor program" being activated in this experiment is therefore not a pure or independent motor program. How can we be sure that this is a motor center, and not just a pain "center" that convinces the rooster he is being attacked? How can we be sure that we are not stimulating a memory, or causing the rooster to hallucinate that he is being attacked? We could account for the same behavior by interpreting the experiment as an interference with the rooster's *experience*, rather than with a hypothetical "motor program." In the Russian view, with its emphasis on "afferentation," this would be the preferred interpretation, since there would be no question of the

"purity" or isolation of a part of behavior, and therefore no need to account for the existence of coordination which contradicts the supposed isolation. In the West, "experience" is not considered to be a quantifiable, proper matter for science to deal with, and so by default the behavior is interpreted as being essentially "motor" controlled.

A related idea is that there is no merely passive "receptor" system, but rather an active analyzer system, incorporating effector links.[6]

The very concept of behavior implies coordination or orientation. The fragmented or isolated movements that are favored for study in the West, because of their purity or simplicity, have been denounced as "the nearly artifactual" results of vivisection, in the Soviet literature.[7]

Coordination implies three kinds of image, and apparently involves the interaction of three general parts of the nervous system. (8) An image of the space in which the behavior is to take place is necessary, and the occipital-parietal area of the brain is the part of the brain most directly involved in this. An awareness of the position of the limbs and the general attitude of the body is also necessary and the posterior region of the hemispheres is related to this function.[8] The sequencing, goal-direction, and meaning which are necessary for behavior to exist, are largely functions of the frontal part of the brain. This sequencing process, for example, makes it possible to perceive rhythms, or temporal patterns,[9] but this process is also fundamental to all behavior or perception which persists or develops meaningfully through time.

The organism then has a model, or image, of the space in which it will act, of its body's relation to this space, and of its intended behavior or its goal. It is this *intention image* which very clearly distinguishes the Soviet approach

from the ordinary reflex theory in England and the U.S. Anokhin has condemned the ordinary theory of the "reflex arc" as an "outstanding failure," which "shows the dualism of its creator" (Descartes), and "distracts from a materialist solution to the problem of purposiveness."[10]

This intention image is the means for regulating behavior--for "collating the actual and the intended"--and is sometimes called the "acceptor of action." That is, the action is refined, until the perceived result of the action corresponds accurately to the guiding image of the desired situation. Besides its usefulness in explaining the regulation of motor behavior, the mental image is also used to explain the feedback control of sense organs. The Soviet view of the function of the mental image in perception resembles some of the interpretations of Gestalt psychology, but the approach is fundamentally Marxian, in emphasizing the objectivity of the image, rather than Kantian, in looking for subjective or arbitrary tendencies or limitations in image formation. The Soviet theorist often emphasizes that we can always escape from old perceptual habits and mistaken hypotheses by having new experiences, and that the source of the organizing process is in the object, in its "objectness," and not in any formal tendency of the perceptual apparatus itself.

This difference between Gestalt and Dialectical theories of perception is very important in the practice and planning of science. A current idea in the west (consider the theories of Monod and Stent) is that basic scientific knowledge has gone nearly as far as it can go, so that no more radical discoveries should be expected or sought. This reasoning is partly based on the Gestalt or Neo-Kantian idea that our "cognitive apparatus" has severe limitations on the kind of things it can know.** The dialectical Soviet view is that radical change in fundamental

science will always remain possible, and that the material world itself if undergoing essential, basic changes. In planning, this means that basic or general science will continue to be funded at least as well as it is at present. While a Western attitude has been "analyze now, synthesize in future generations," the dialectic attitude suggests that "we need a Whole now, to achieve a better Whole in the future."

If *image* and *meaning* are given priority over *movement* and *form* in describing the functioning of the brain, then science would seem to sanction the transformation of labor into perception. This is, in fact, an explicit trend and policy in the USSR. Recognizing that perception requires interaction with the object, we might say that "consciousness is action." Again, it is a belief of this sort that is responsible for the pervasive interaction of politics, culture, work, and science in Soviet life.

Besides regulating movement, the mental image represents an accumulation of experience, or a "history." It is sometimes referred to as a hypothesis, that is, as a guess or expectation about an object or event. Recalling the functional components of the mental image--space, body-awareness, and sequencing--it is obvious that memory, the history of experience, will be most directly involved in the sequencing aspect of perception. In meaningful, sequentially patterned behavior, the organism is interacting with its environment, and in a sense is "testing its hypothesis" about that part of the environment. If something fails to meet its expectation, that is, if the organism is confronted with a novel thing, it will have no ready-made plan of action, no adequate hypothesis, and so will have to mobilize his perceptual apparatus to find out more about the novel thing, and to create a new hypothesis-image. This process is known in the USSR as

the "orienting reflex," and will be described in detail in the next chapter. When a new understanding and a new image have been achieved, the organism has linked the parts of a novel arrangement into a new meaningful configuration, which may be a useful discovery for the organism, such as a new kind of food, or a new way of producing food. This is the general Soviet interpretation of how a "conditioned reflex" is formed--the important idea is that the organism has recognized a problem, and solved it by discovering a meaningful relationship.

It is worth noting that the Marxian theory of scientific discovery (and of education) is identical in form to the Marxian theory of brain function--in both, there is an emphasis on purpose, deep reorganization, and complex perceptual interaction with the material. In the west, scientific discovery is likely to be explained by reference to logical processes (deduction, induction) or by the idea of a "lucky" choice of a good hypothesis, with none of these relating very deeply to theories of brain function, except that the "computer" theory of brain function is popular, i.e., the brain is seen as a logic machine. In the west, the difference between human beings and animals is usually described as the absence of certain "programs" in the animals' logic machine. The Marxian orientation more typically is concerned with the common or universal characteristics of organisms, and then accepts as special anything that goes beyond the general rule.

The image of space, and spatial relationships, must be subject to the mental "sequencer," if the organism is to move through space with awareness. The mental construction of an object, a "meaningful configuration," described above, applies to the organism's understanding of all aspects of reality. A process that begins as a sequential scanning is able to achieve a stable simultaneity, an

"objectness," a spatial quality.[14] The stored features are related in a certain way so that they can be checked against the real object, and this image thus achieves a spatial quality so it can be used in later, or "higher order," sequencings.

Having established objects, useful configurations of objects can be made by this same process, which is not higher in any important sense now that it is applied to images which have achieved the stability[15] of "objectness." The stabilizing effect of objectness" on evaluations of sense data[16] is a major step in functioning, but all subsequent constructions (configurations of configurations) are just extensions of this basic process.

This is important to mention because of the common western belief that intellect, abstraction, and generalization are very special achievements, probably genetically unique when they occur:

> I don't know whether there is a common animal ability to manipulate images and generalize. In fact, I doubt it very much. Thus the kind of "generalization" that leads to knowledge of language from sensory experience seems to me to involve principles such as those of universal grammar as an innate property, for reasons I have explained elsewhere, and I see no reason to believe that these principles underlie generalization in other animals. Nor do I think that the kinds of generalization that lead a bird to gain knowledge of how to build a nest, or to sing its song, or to orient itself spatially, are necessarily part of the human ability to generalize. (Noam Chomsky, 1972.)

Chomsky's use of quotation marks around "generalization" is very much like the Behaviorists' use of quotation marks around "mental."

The Marxian position is committed to the objective existence of generality: For the "Dialectic" to operate in matter, without an overseeing God, the meaningful units (such as thesis and antithesis, and the social classes, etc.) must exist intrinsically in matter, which is just to say that generality has objective existence. The Marxian theory of perception appropriately incorporates the generalization function at a very early level of brain function, both in ontogeny and phylogeny. To the extent that the regulatory mental image doesn't constantly arouse the full orienting reflex because of slight disparities between intention and achievement or observation, it is generalized. A general class of achievement, or object or situation, will satisfy; further refinement may be undertaken, but only for a particular reason. The organism otherwise would become immersed in constant refinement of behavior. Since the orienting reflex becomes stronger at higher evolutionary levels, we can think of evolution as being away from *facile* generalization, and toward a more detailed understanding of matter. At these more refined levels, mistakes are more possible if sensory contact isn't maintained. This point relates to the Marxian belief that valid knowledge derives from practice and workability (Engels), and also to the Marxian idea that cultural forms and beliefs represent a superstructure, rationalizing power relationships or modes of production. If knowledge is derived deductively, rather than from practical experience, it is likely to be empty and mistaken, rather than a true refinement of knowledge. (If humanity were unified, in cooperative production, then culture would be part of the productive base; this principle

is currently being recognized by the official policy statements of the Soviet Union.)

One aspect of mild "psychopathology" probably relates to the simple fact that a child can become accustomed to looking exclusively to others to resolve questions, rather than being carried by the orienting reflex directly to the relevant practical, material reality for his answer. Despite the possibility that "culture" might reinforce this kind of dependency or insecurity, culture is considered by Marxian theorists (including those specializing in brain function) to be a uniquely valuable human achievement. While animals are generally unable to go very far in the direction of a refined understanding of nature and of themselves, it is essentially an intensification of this basic "animal consciousness" which makes culture and rapid intellectual progress possible (as well as making false cultural rationalizations possible). The difference seems to be in the degree to which human beings are able to deeply restructure their mental images when their discrepancy with reality may be only slight.

It is this model of brain function which was foreseen by Marx when he said that words were the "names for mental ghosts," in his refutation of the old "nominalist" theory of language. It may have been this basic idea that the words of language have a mere "naming" function in relation to the various structures of consciousness that led Stalin to write his famous policy statement on linguistics, in which he declared that language was properly to be considered as a part of the productive base, rather than as a part of the cultural superstructure which must be revised by a revolutionary state. (It is only very recently that consciousness itself has come to be treated as a "primary productive force.")[17]

Since all perception involves "recognition" in some way, generality is an essential part of perception, and is not a "special" problem for language. Language behavior is a popular subject in Soviet physiology, and as in other behavior studies, afferent processes are emphasized. The perception of phoneme sequences, and the relation of these acoustic processes to the "intention image" are important subjects for investigation. The Soviet understanding of "verbal behavior" must not be confused with Skinner's use of the phrase, since Skinner and many American behaviorists and nerve biologists insist that no "subjective" events can be included in their scientific explanation, while the image is the central event for the Pavlovians. (Pavlov's respect for self-observation is illustrated by the story that he carefully dictated to an assistant all of the physiological observations he could make as he was dying, and a visitor was sent away with the response to his knock: "Pavlov is busy, Pavlov is dying.")

The common schizophrenic language disturbance, typically involving undirected, punning speech, has been interpreted as a disturbance of the deeper image levels and a shift to the acoustic levels of memory, with the result that meaning is lost to the degree that the linguistic forms themselves are concentrated on.[18] This is one of the ways that the broad theory can provide a foundation for practical work. Energy processes are usually assumed to be the basis for the disturbed function; for example, serum from schizophrenics disturbs the carbohydrate metabolism of chicken erythrocytes, increasing the lactate/pyruvate ratio.[19] Efficient searching of the memory would require efficient energy production; other aspects of this will be discussed in the next chapter, on the "orienting reflex."

A very different kind of image disturbance was reported by Luriya in his book *The Mnemonist.* The book

told the story of Luriya's study--over a period of many years--of a man with an extraordinary memory. The man was able to memorize long lists of objects which were read to him, and Luriya found that the man could recall these lists even twenty years later. The mnemonist said that he imagined himself walking down a Moscow street, placing the objects along the way as they were named to him by the psychologist. The only mistakes he made were of a perceptual nature--e.g., "I didn't notice the red ball because I carelessly set it against the red was of the building I happened to be near." The mnemonist experienced synesthesia of vision, sound, and textures, and felt that memories were localized in his body--for example, instead of having a word "on the tip of his tongue," he might "have it" in his left index finger. The intensity of his imagery interfered with his understanding of language, not apparently as schizophrenia or aphasia interfere, since he was likely to take figures of speech literally, and to be distracted from the actual point of the statement, which he might otherwise have understood normally. As a result, he was never successful in holding an ordinary job, and worked as a performer. The Pavlovian factors, balanced, strength, and mobility of the nervous system provide a framework for understanding this peculiar state.

Anokhin has reviewed a model of cortical/subcortical interaction which is now widely accepted and which offers a simple way of understanding these disturbances of the language/image relationship. Anokhin's image is of a river flowing through the brain stem, a variable pattern of ascending excitations reflecting the given biological state. In this view, a weakness of the activating system would tend to excite the cortex in a fragmented way, as a nearly dry river doesn't even fill its own channel. This image would explain the fact that

"leucotomy" as practiced in the west eventually leads to a state of excessive verbal "concreteness," or rather verbal rigidity and lack of imagination. The Soviets have done a considerable amount of study of the use of substances to improve memory and mental performance, and their results are typically attributed to the facilitation of excitatory conduction.[20] An imbalance in the other direction, toward excessive subcortical excitatory, or deficient cortical control activity, would presumably produce intense images, poorly calibrated with reality. Even conditions such as asthma have been interpreted as a weakness of the higher inhibitory functions.

The Marxian and Soviet view, that generality is an intrinsic part of perception, provides no basis for the belief (so common in western countries) that the progress of knowledge toward higher generality requires the fortuitous occurrence of "geniuses." Creativity is treated as an essential human trait, part of the human need for self-realization through productive work. Social support, including education, is considered to be the factor which causes great differences in creativity and intelligence, and not genetics. A genetic theory of intelligence is considered to be a mere rationalization for racist practices.[21] Visual imagery is considered to be the basis of creative intelligence,[22] and as such is studied with the intention of finding principles that can be used in education. Emotions (e.g., as measured by the galvanic skin response[23]) are also considered to be an important component of inventive behavior, and are viewed as part of the image-forming process.

IQ tests are not widely used in the Soviet Union, since the IQ is believed merely to reflect the level of social opportunity (which can be determined in other ways), but some very interesting studies have been done to determine

the effect of socio-economic status on intelligence. Children in some asian-USSR towns were given IQ tests in 1929, and averaged about 35 points below normal. Recently children in these "retarded" areas were tested, and were found to be approximately equal in general mental ability to children in Moscow. In numerical and verbal ability they were slightly behind the muscovites, but in visual memory and interpretation of mirror images, they were superior. These differences are attributed to the continuing differences in their life situations.[24]

The importance of the visual image and other "subjective" events such as emotion is summed up in the idea that it is useful to compare computers with the brain, not to see the brain as a computer, but just as one method of seeing what is peculiarly human about our brain and nervous system, and sometimes to get ideas to improve the design of computers. For a very long time, Russian scientists have held the attitude that the world is infinite but knowable. As long as a computer is just a finite set of circuits and programs it can't be considered seriously as a model of the brain.

*The Latin cultures are generally very visual, with great painting traditions. It would be interesting to consider how this might influence their scientific culture.

**Kantians often use the ability of bees to see ultraviolet light to argue that we are condemned to know only a limited world. George Wald discovered that people can see ultraviolet images clearly, after their lenses have been removed in cataract surgery; the small mass of the bee's lens makes its eye more sensitive to ultraviolet, so this supposedly "essential" difference is only a relative difference.

CHAPTER 3
THE ORIENTING REFLEX

What sort of person, or culture, is it that sees "exploration" as the strongest and most basic reflex of the organism? It obviously can't be one that fears new knowledge, and it presumably would be one that values science, progress, and freedom to grow. Starting from any holistic position, it doesn't seem peculiar to view curiosity, an instinct for exploration, or a desire to perceive, as the fundamental tendency of an organism. However, the western traditions in psychology and biology are not holistic, and the tendency toward integration of knowledge, as far as it exists, proceeds by correlations of accumulated facts, level by level, as if science were blind to wholes. Both the Marxian and the Russian traditions in science have largely ignored the distinction made elsewhere between psychology and biology, so that biological thinking is informed by the awareness of human needs and possibilities, and psychology is not thought of as being in any sense un-biological. The Marxian attitude is to work from wholes, and from futures or purposes, as interpretive frameworks, toward the so-called concrete facts and experiments. The Soviet concept of the orienting, or exploratory, reflex is the most important single holistic "informing principle" in biology and psychology. It comes close to being the definition of an organism. It is not only important in this logical or philosophical sense, but it is frequently described as "having an intensity greater than any other activity of the organism." It dominates not only because it is holistic, but because it can be very strong, in

the simplest physiological sense. There is nothing tenuous in this kind of holism.

Pavlov described this reflex as the "what is it?" reflex. With more detailed knowledge of the brain, the reticular activating system of the brain stem has come to be considered as the most important location of the integrating and exciting processes in the orienting reflex: For example, aminazine, a chemical which selectively inhibits the reticular formation will block the reflex. But it is distinctly a reflex of the whole animal: Cortex, hypothalamus, sense organs, motor and autonomic processes are integral parts of it. It is the thing that makes learning possible, and every part of the organism participates in an appropriate way. Many western researchers have claimed that conditioning doesn't always involve the cortex, or that individual reflexes such as the heart reflex are separable things--"when you call the dog, first comes the pulse, then comes the dog." These points are denied by all the leading Soviet workers, and considered to be mistakes of methodology or interpretation.

The image, as already discussed in the preceding chapter, is the central part of the orienting reflex. An unfamiliar sound, for example, will arouse the animal so that all of its senses bear on the thing producing the sound, so that it can construct an image or "reflection" of the thing in its consciousness; if the object (or required behavior) is familiar, the animal will be able to match its image with what it is perceiving so that recognition of the thing or execution of the action is immediate. The animal knows what to do with the object, and doesn't have to concern itself with investigation of it. A familiar environment frees the energies for other purposes, which (especially in apes and humans) may be a search for unfamiliar things. Some experiments with children suggest that an image emerges early in learning, and that it controls the subsequent

functioning of the motor system, which is gradually "assimilated," and developed into a habit.

As familiarity and experience increase, the world becomes ampler for the organism, its range increases. This is exactly the opposite of a view that says that the animal, with each increment of learned behavior, becomes more specialized and limited. Learning is not a closing, but an opening of possibilities. The "motor" theory, which neglects the fact that the organism is always oriented with regard to its environment, must see every learned precision as a restriction of the organism's freedom. In the West, we are constantly told that "we must give up some freedom to attain mastery of" some behavior or technology which is desirable. On the social scale, we hear that specialists must not venture beyond their "area of competence," and that political specialists know what is best for society. American Behaviorism is a fine ideology for a society that wants to combine authoritarian government with a system of specialized training for specialized jobs, because it claims that finely controlled behavior must be specialized and exists as a constraint on behavior. The error, of course, is that they ignore the fact that there can be no behavior without orientation, and general understanding of the environment (the relevant world) is part of fine control of behavior. Marx's thinking was based largely on his perception of how people were diminished and degraded by work that lacked meaning for them. More recently it has been found that workers are more productive when they understand the part they play in the whole production process. The mastery of a skill is very literally like the opening up of a new space, an extension of the lived world. An ability to perform a certain action is an ability to perceive the proper relationships and sequences, and is an openness of one thing to another. All

recognition has some generality, and generality is like "internal space," the possession of adequate images.

There may be very simple anatomical or physiological reasons for the fact that a discrepancy between the mental image and the environmental stimulus leads to such an intense reflex, such an energetic mobilization of the entire organism to deal with the novelty. This question is right at the border of present knowledge and speculation. It is reasonable to look for the most intimate connection possible, between energy production (metabolism) and energy use (experience, in its broadest sense). It is now common to look for metabolic disturbances in connection with perceptual/behavioral problems. In some sense, we can think of the image-discrepancy as being represented on the tissue level as a disturbed resonance, a structural distortion--the physical details of this are highly speculative, but the Marxian viewpoint expects a higher holism to exist, even beyond the level which sees an organism as "a desire to explore." Whatever the mechanism, it probably involves very subtle states of matter.

It we think of the organism as an energy system, holding its world-image in consciousness, it's reasonable to guess that a unified, generalized picture of the world will take less energy to support than will a jumbled, chaotic collection of images--and certainly the recall of the appropriate image to interpret a stimulus will be easier if the world-image is highly organized. A higher degree of holism would be the existence of a tendency toward completeness, as part of the exploratory reflex--a desire for a view, not just for isolated or random images. This is usually assumed in the discussions of the orienting reflex, but to make it explicit makes it easier to see how the orienting reflex relates to other kinds of behavior, such as eating, sex, and

defence. The distinction between "self" as mental images, and "world," as the source of novel perceptions, becomes more important in those other more specific reflexes, but we can still see in them the general form of the basic orienting reflex. Each of these reflexes is holistic, in the sense that it mobilizes the entire organism for a particular purpose.

We can get some insight into these reflexes by considering the degree to which they are homeostatic in effect, as opposed to being "heterostatic" or "hetero-dynamic" in effect, that is, whether they restore a previous condition, or lead to growth and development. The orienting reflex is always a growth reflex, since it allows the self to approximate itself to a novel aspect of the world, becoming something different in the process of assimilating strangeness. The defense reflex, on the other hand, is highly conservative or homeostatic, because its purpose is to withdraw from an expected threat, and to return to a previously known safe pattern, without a new synthesis.

The eating or food reflex is mainly homeostatic, though of course it has a growth component. The desire for a specific kind of nutrient which results from a lack of it is especially interesting, and reveals something about the nature of hunger in general. An image of the desired type of food, or a preference for that kind over other kinds if several are available (which requires an image too, though it may be weaker than the image that directs an active search) implies a discrepancy between the perceived present state of self, and a mental image of the whole self. The whole self is the one without the specific craving. This discrepancy is like that experienced when a question is being asked: In the mental world (the self, but with reference to external space, rather than the body) something is perceived as incomplete, and the question seeks completion. Questions can be conservative, looking for completion of the old world, but

they more likely indicate an openness, seeking a new synthesis. A desire for food is thought of as conservative or restorative, simply because the body seems simpler, and is not usually seen as being in evolution. We might, though, imagine an evolving body, craving new nutrients, or new ratios of nutrients, as part of a developmental process. So we needn't think of the "eating reflex" as being strictly conservative. The desired item, the focus of the "discrepancy," is analogous to the novel stimulus in the orienting reflex. The desire for completeness in the body is like the desire for wholeness in the perceived world. Even in exploration, the object is modified a little--but in eating, the object is more completely assimilated to the body, rather than the body to the object.

The "sexual reflex" similarly can be either conservative or developmental. Before exploring some of the things involved in it, it will be useful to consider an experiment involving the use of images in training people to get voluntary control over an autonomic response. Lisina (in 1957, long before "autonomic training" and bio-feedback became respectable in the U.S.) found that bio-feedback makes it possible to control a vascular response by acting through the orienting reflex, and that a response which couldn't be formed through "ordinary" conditioning became possible when awareness was made part of the procedure, using bio-feedback (a light signaled when blood vessels in the fingers were dilating). Learning not only requires awareness, but images are directly able to evoke some of the autonomic responses that are appropriate for that situation. For example, thinking of a frightening event will make the heart beat harder; thinking of heat can make blood vessels in the skin dilate.

The autonomic components of the sexual response are obvious, but what is less well known is that hormones

are delicately regulated by the brain, as part of the organism's response to its sexual and social environment. For example, women living in a group synchronize their menstrual cycles, men's whiskers grow faster when they look forward to sex (because their testosterone secretion increases), and men's testosterone secretion increases both in response to a monthly cycle and in response to social success. This hormonal intensification might be thought of as being analogous to the general exploratory arousal, as part of a holistic physiological activation process, but that would leave unanswered the questions "why desire the opposite sex rather than a shoe or a frog?" and "how does the opposite sex satisfy this desire?" and "how does orgasm relate to image?" If the sex response is a special, isolated process, it would be sufficient to say that we must have an innate image of the partner, and of appropriate behavior, etc. However, this comes close to the idea of "motor programs," and it also fails to account for the personal and exploratory dimensions of sexuality.

Using some of the principles established in other reflexes, we can get a highly generalized picture of the "sexual reflex," which is also highly empirical in the sense that it doesn't go much beyond what we commonly experience in the sexual response. In the "food reflex," we saw that we could avoid the mysterious motor programs and drives of the mechanistic behaviorists, just by recognizing the perception of "something lacking" in the body (which could be fullness in the stomach, adequate blood sugar, vitamin C, etc.). This requires the perception of a discrepancy between the presently perceived body, and the known body (as it should be). The process of resolving the discrepancy between these images is generally similar to that in the orienting reflex, but the behavior is appropriately different. If it is the body and the experiential uniqueness of

the particular sex partner that we desire, it is obviously desired because it isn't possessed, and this implies a discrepancy between the self-image of body-and-experience, and the image of the desired one. The autonomic patterns (among many other things) of the sexes are distinctly different. If we apply the "structure" of the orienting reflex, in which the mental image or the "action acceptor" approximates itself to the form of the novel stimulus, then we would in our (possibly subliminal) gestures and images and autonomic processes, be approximating ourselves to the form of the opposite sex. Only certain forms (such as vascular distribution) can be strongly participated in by our body, and these seem to be the points that have been used to advantage by the opposite sex. We still have our knowledge of our own body, and what its wholeness requires--as in the eating reflex, we *at least* conserve our body. Since our body has nervous regulators of hormone level which accommodate the body to changed conditions, the image's movement toward, say, femaleness, would be balanced in the male by a secretion which increased his maleness, and probably also by various compensatory nervous changes. The key idea is that our autonomic emotional system is part of all of our imagery, perception, and discovery. The only real novelty is the suggestion that we "autonomically conform" to the perceived person in sexual ways just as we do in other emotional ways--we tend to respond to fear with fear, and to joy with joy, etc. This is just saying that when we appreciate the opposite sex, we perceive to some extent what it is like to be that sex. The hormonal balancing would be a homeostatic process, when considered from this point of view.

In both the orienting reflex and the sexual reflex, a discrepancy of images would lead to very intense arousal, but while the orienting reflex quickly leads to learning

(approximation of the mental image to the novel object) and to extinction, the body in the sexual response is exaggerating itself, intensifying the image-discrepancy and the excitement. We obviously don't forget who we are just because we are feeling what it is like to be the other person, which is simply to say that we feel a tension between our bodies, between novel and known.

When the body, with its conservative tendencies, is involved, closeness of the relevant thing--threat, food, or mate--makes the need clearer.

If we think of the image as including autonomic nerve processes, it is not too strange to think of the orgasm as being an act of discovery regarding the nature of the opposite sex and of the particular sexual partner. If this is an appropriate description of the orgasm, then the sexual response is really a special case of the orienting reflex--perception of novelty, arousal, discovery, and inhibition being the general structural components of both. In many cases, satisfaction of curiosity or extinction of the orienting reflex leads to sleep, because of cortical inhibition. It would be interesting to compare the EEG and other patterns in the sleep which follows both sexual orgasm and extinction of the orienting reflex.

The sudden interpretive "twists" that occur just before and during orgasm illustrate the close involvement of mental images with autonomic "image" and function. This involvement exists in all behavior.

The perception of, and desire for, the mate's experience of the world would have its own particular rules, but would not be entirely separable from the "body desire."

Whatever the precise form of the sexual reflex turns out to be, the Marxian aim is to understand it as meaning, as "afferentation," and not as mere motor behavior. Just as Anokhin has clarified the identity of the orienting and the

exploratory reflexes, we can see the orienting-exploratory reflex as a paradigm for all mean- ingful behavior.

The orienting reflex is known to exist in fish, turtles, and birds, as well as in mammals. Since the forebrain is a development from the olfactory lobe, it is interesting that in developing young animals (e.g., puppies and monkeys) the orienting reflex emerges earliest in relation to smell; the olfactory system ("analyzer") is the first to develop functionally and morphologically. As the tactile, auditory, and visual functions of the cortex mature, so do the responses to the corresponding stimuli. In young puppies and prematurely born children, the autonomic components of the response are much stronger and slower to extinguish than when the cortex is more mature. So even though more primitive tissues are essential for activation, the reflex is largely cortical.

Some of Anokhin's descriptions of the orienting reflex are useful for understanding what is now the dominant Soviet theory in physiology, and for seeing how the orienting reflex relates to other processes.

He has given four characteristics of the orienting reflex which apply to any holistic activity: It is centrally integrated, it is exclusive, it has an adaptational effect for the organism, and it includes feedback. Anokhin emphasizes that central integration means that "there cannot exist a 'conditioned reflex of the heart,'" or of other isolated components. "A fragmented, isolated approach results in an immense number of experimental errors, in particular, when a component of a reaction taken separately, often for methodological reasons, is considered to be some special conditioned reflex."

The "exclusion principle" means that every holistic activity tends to be the only one present at a given time. He suggests that this mechanism has evolved simultaneously

with the organism's complexification which increases the number of its systems' functions.'

Anokhin stresses that afferent feedback is an intrinsic part of every holistic activity, that it has the status of the "fourth link in the reflex." This means that "it is impossible to isolate the afferent feedback from the total action which begins with the reflex arc and ends with the afferent feedback." (This process was outlined in the preceding chapter.) "The orienting reaction cannot be terminated in its process," since "such interruption would automatically yield information regarding what is going on outside of the organism."'

The exclusion principle can be elaborated a little farther. If the orienting reflex is very strong, it will inhibit all other present acts. But it can also be assimilated by the ongoing activity of the organism, so that the excitation from the orienting-exploratory reaction summates with the activity that is dominant at that time. There will be just one activity, but its intensity will increase. Under other conditions, there can be a transformation, so that the reaction to novelty brings out a concealed "dominant," and suppresses the activity that was present. The defensive reaction is the one that most frequently assimilates to itself the excitation of the orienting reflex. This transformability of the orienting-exploratory reflex into a defensive reaction has a parallel in early development. Early painful experiences, "during the period of formation," can lead "to a prolonged pathological reinforcement of some reactions and the weakening of others which exerts an influence on the whole life that follows" (Obraztzova, *et al.*). In puppies, early trauma leads to behavior dominated by the passive-defensive reflex, and suppression of the exploratory reflex in particular. It is assumed that something equivalent can occur in humans.

CHAPTER 4
REFLECTING CONDITIONS

At first, I thought it might be best to avoid a direct approach to Pavlov's development of the idea of conditioned (or, rather, conditional) reflexes, because everyone thinks the idea is already well-understood in our culture. But maybe it is better to consider our idea of the "conditioned reflex" as an obstruction to be cleared away, before going on to explore the tradition of Pavlov.

In English, the word "condition" has two groups of meanings. One group clusters around the idea of "stipulation," as in "he accepts the proposal with certain conditions," and another cluster has to do with something closer to a thing's state of being, as in "the car (or athlete) is in good condition." Our English word derives from Latin for "speaking together," and in Russian there is a word, *uslovni,* with a similar origin relating to speech and stipulation. However, Russian has also adopted the Latin-based word, *konditsiya,* with its meaning limited to our "state of being" cluster, making it impossible to confuse the two meanings: Air-conditioning and athletic conditioning use the Latin-derived word, while contractual and linguistic conditions use the Slavic word. In Pavlov's work, the "conditional reflex" was understood as the "stipulated or agreed-upon (*uslovni*) reflex," but this essential point has been almost entirely lost in a false translation. Watson presented himself as a student of the famous Pavlov, and argued for an unconscious psychology, with the result that our culture has lost the meaning of the century's greatest work in psychology and brain physiology. (Sometimes I wonder whether J. B. Watson wasn't

vacationing in Bermuda during the time he claimed to be studying with Pavlov.)

Pavlov was the son of a priest, and studied at a seminary school, so he was thoroughly saturated with the Greek-derived ideas of the Eastern Church. For Pavlov, the world's essential property is that it is full of potential, and that we will know more in the future than we do at present. This centrality of time permeates the tradition of Pavlov. If time is real and the world is the source of knowledge, then science is seen as a basic life function, in which the brain is the organ for knowing the world and maintaining an equilibrium with it. The essential feature of the conditional reflex, as understood by Pavlov, was its temporariness; if it is a recognition of a temporary conjunction of events in the world, intelligence requires that it not persist longer than the condition in the environment does. But when learning has to do with the way the world actually works, one insight is enough to fix the knowledge forever; Pavlov said that when a cat learns how to open the latch to its cage, such learning has taken place, and the cat is doing something equivalent to science. (He also believed that such permanent, scientific learning was eventually incorporated into heredity as the instincts.)

In the West, our idea of the "conditioned reflex" has been exactly the opposite: we have emphasized its difference from insight-learning by ascribing to it a kind of brainless sluggishness, in which the role of time is reversed--it is slow to form, and slow to decay, but sure to decay, without regard to whether it is insightful or merely arbitrary.

Besides giving us a mistaken interpretation of Pavlov's work with the conditional reflex, the tradition started by J.B.Watson and continued by B. F. Skinner helped to make psychology remote from physiology as well as from

morality. Skinner felt that his work had moved us "beyond freedom and dignity," and he saw the brain as such a neutral ground, or blank slate, that he said that the maternal contribution to the developing fetus is "nothing but her genes." To distinguish psychology from biology, he eliminated physiology from biology, leaving nothing but a timeless and rigid genetic determinism below his malleable "environmentalism."

Pavlov recognized that there must be attention before learning could take place, and that the availability of brain energy was specific, and appeared according to the needs of the organism, and was provided by the hereditary instincts. Thus, when an animal attends to a new thing or situation, or when it explores, it is using a specific brain energy: He spoke of an instinct for exploration, for science ("a truth tropism"), for liberty, and dignity. The integrity of the organism requires opportunity for exploration, for freedom, etc., and Pavlov pointed out that psychiatry must treat mental patients with proper concern for their needs and rights. (The California researchers who found that rats' brains grow when their environment is enriched, and that the effects increase with subsequent generations, probably didn't know that they were validating two of Pavlov's basic doctrines.)

Pavlov was clear in saying that his purpose was eventually to explain how human consciousness works, so--even though he began his studies with the "eating reflex" because "nutrition is the most essential link between the organism and its environment"--it is natural that his group would look for ways to study questions such as the "biology of intentions," the perception of novelty, orientation, exploration, etc. Their major achievements can be seen as growing from Pavlov's observation that there is a

specificity of attention deriving from a specific energizing of the brain.

Pavlov's concept of sensory analyzers is one part of the idea of specific, energized attention; the sensory analyzer includes the sense organ, such as the eye or the vestibular apparatus, and related parts of the brain. It is emphasized that sensing is an active, intelligent process, in which features of the world are analyzed, selected, and linked with the organism.

We hear most about the simple associative learning of Pavlov's dogs, but Pavlov went from the study of simple association to the investigation of learned sequences, or Dynamic Stereotypes. To understand a thing, its properties, besides being singly "linked" with the organism by the sensory analyzers, must be linked together with each other, until they can be grasped simultaneously. This simultaneity is called "objectness."

This composed simultaneity is an image of a thing or a process in the world. A goal of the organism is held in mind as such a simultaneity, and is the organism's criterion for completion or correctness of action. Anokhin pointed out that the "stimulus-response" "reflex arc" was incomplete without such a model of the appropriate reaction, and he called this model "the acceptor of action." These mental images, acceptors of action, are both models of intention, and models of what is known; novelty exists whenever the acceptor of action lacks any feature of the perceived environment. Intentional actions mobilize the organism's energy and focus it toward completion. (A story about Einstein illustrates: Finishing an article, he and a collaborator searched for a paper-clip, and Einstein found a bent one, which he tried to straighten. His collaborator found a box of paper-clips, and Einstein took one, and used it as a tool to finish straightening the bent one. He said he

found it hard to stop a project once he started it.) In exploration, it is novelty which excites the brain and mobilizes the organism for further investigation. The exercise of the exploratory reflex seems to make more energy available. As long as the world remains a source of new knowledge, the brain will react to novelty with a continued increase of exploratory energy.

The human frontal lobes allow us to construct very complex systems of images, or acceptors of action. Pavlov opposed the "biologizers" who wished to ignore the importance of human history and culture in the development of our capacities--people who attempt to draw political conclusions from what they claim are human instincts of aggression, territoriality, etc. Pavlov called the first levels of constructions, closely tied to the sensory analyzers, the "first signal system." Language and the complex systems of meaning that make up culture (which are possible because of the unique development of our frontal lobes), Pavlov referred to as the "second signal system." Science requires that we account for consciousness in biological terms as far as is possible, but consciousness also includes historical and cultural influences, and our biological conceptions must be adequate to account for the existence of all those things which are simply historical--so many of which are arbitrary, and therefore temporary, and to be grown out of. The "biologizers" often speak of "genes" for aggression and militarism, because they strongly wish to deny the reality of social-historical processes, but Pavlov argued that moral ideas can change history, and historically determined behavior.

Some psychologists have argued that psychological "conditioning" can be used to "brain-wash" people into accepting an authoritarian system. I think it is important to

remember that Pavlov understood the conditional reflex to be an intelligent brain process which allows the organism to adapt itself to the world, but also allows it to modify the world to suit its needs for freedom, dignity, morality, and mental exploration.

CHAPTER 5
DOUBLENESS AND PERSPECTIVE

After talking about the unifying, holistic nature of brain and organism, we should consider what it means that we have two similar, but "opposed" sides. Even an earthworm has two symmetrical sides, but as we go up the evolutionary scale, the symmetrical central nerve-brain tube of the chordates not only enlarges at one end, but it also increasingly segregates into two bilaterally symmetrical lobes, the cerebral hemispheres.

Is there a function which is being "simplified" by increasing two-sidedness, as increasing cephalization (head dominance) makes possible increased differentiation and control and subtle coordination with the environment? According to B. G. Ananyev and others, two-sidedness of the brain is involved in our time and space perception and regulation: Perception and control are a unitary process, but the unity is based on the interaction of two halves. Depth perception, for example, is the creation of a perspective by the interaction of two or more slightly different images which separately reveal no perspective. If we use only one eye, we can construct a perspective, but in this case we are more dependent on movement, and the combination of images collected over a period of time. (Incidentally, the recognition that stereoscopic perception is a central process which can be independent of external, binocular triangulation, is a revolutionary insight which will tend to purge away mechanistic and Cartesian ideas of consciousness.)

Separate control of the two sides of the body would seem to require separation of the imaging control

system--and as we have a doubleness, a perspective, *"within"* the body, we must (as world and body-control are integrated) have a similar doubleness, perspective, within the world. Rhythmic alternation or wave-like motion won't do for animals that manifoldly manipulate the world, changing it. Besides using the two-sided system to control our body in space, we use it to construct a perception of time. If we could only record the perspectives delivered to our brains by movement, it seems likely that we would be locked into a relatively rigid view of space. Because we incorporate a generator of perspectives within our two-sided nervous system, we experience a relative fluidity of time images, and this time-imagination makes our attitude toward space more flexible.

Wilhelm Reich believed that a kind of peristalsis was the basic biological movement, and showed how ideas relate to blocks to this movement. Although the Reichian theory is as compatible with Marxism as with Freudian theory, in its popular American and European versions, there is a failure to integrate sex and culture, vegetative process and insight: Wave-like rhythms are given priority over quickly flickering intuitions. Yet sexual rhythms can be light and cognitive, quick as a flash of knowing, not heavy, lumbering or "conditioned" (in the current sense of being "reactively imprisoned in an evaluative pattern"). Nevertheless, as Chernigovsky has demonstrated, visceral and vegetative processes are diffusely represented in the cerebral cortex, suggesting that we haven't evolved great powers of visceral discrimination. More highly evolved beings might be able to write visceral poetry beyond our capacities, but this doesn't imply that there is something intrinsically slow about our energetic processes.

A mechanism which can subtly discriminate the sides of the body into "reference point and measure," "holder and

chipper," etc., can also insinuate itself into complex vistas, "deforming" relationships as it would modulate its movements in making objects.

A scanning with an objective rhythm, a re-scanning with a manipulated rhythm--in place of a mechanically rhythmical time, or a mere responsiveness to the objective order in its surroundings (fitting crawl-swim rhythms into the world) there comes to exist a perceiver who can modulate his own time perception.

The Neo-Kantians see us as being cognitively trapped by our bodies, forced to know the world in an arbitrary, limited way. The Russian tradition sees our body as having evolved specifically to grasp reality in an appropriate way. Neo-Kantian American biologists see the body as an accident, as far as knowledge of the world goes: "Given this apparatus, we can only know thusly." The Russian insight is that evolution is a perceptual dynamic, ever becoming more flexible, able to insinuate itself. The basic adaptiveness is perception and response--a beak, a claw, a gut, a feather, pigment, foot, any biological form, is useless without perception, especially subtlety of perception, adequacy.

Capacity for response (selection of environment) is perception. Selection of an environment can then create a basis for physical selection. Perception is prior to "natural selection," On this basis, we can accept our internal doubleness, our stereoscopic consciousness, as being a highly appropriate way of approaching the world, of getting objective knowledge.

The great majority of our nerves are visual and sensory. Motoric subtlety is achieved by the "afferent" or sensory nature of our cerebral cortical function, that is, by modulating simple motor output according to fine timing (and spacing) of the imaging cortex. Both timing and

spacing (depth creation) are made possible by internal doubleness--perspective creates space (using either time or two perceptual channels), and mental-motoric insinuation, pacing or timing rhythms, create the experiences we have of time. We span a broad present when we have complex rhythms that carry us deeply into a meaningful space. Mechanical rhythms would seemingly disregard the depths of space, and near or far, now and then, wouldn't be so strongly differentiated. With complex and subtle rhythms that can differentiate the present acutely from other times, the uniqueness and fullness of present is perceived as part of the fullness of time, so that we exist in a depth of time as we respond to the depth of space. Our doubleness is a time sense, just as it is a space sense. Space and time are reflected in us.

Seeing consciousness as being both energetic and structural, we can describe the process with an image like this; It's as if "present energy" would leak out of the past and future through their sameness, if we had mechanical rhythms, but would be captured and accumulated to a high level by awareness of change and variety. There may be actual biophysical and chemical events which correspond to this image. This holographic, liquid-crystalline, resonance theory will be discussed separately, but here it is appropriate to mention that there is a simple physical correlate for this image of a "self-stimulating doubleness," namely, that the two cerebral hemispheres are mutually trophic, that is, they activate and maintain each other, just as they contribute to the activation and maintenance of the entire body.

CHAPTER 6
SEXUAL ENERGY AND THE CORTEX OF THE BRAIN

The cortex is the mediator between inside and out. For an abstract person, like Descartes or Sartre or the average American scientist/salesman, all of reality is like a skin between the world and the self, leaving a vacuum for self and for world, except as there is arbitrary interaction in this abstract reality-skin. These are "cortical" people in the sense that their interacting self has very little to do with their body's highly determinate needs; they are the people that Pavlov called "intellectuals," dominated by the "second signalling system," language. According to Pavlov, they aren't quite at home in the world.

The type of person who grasps the world clearly and strongly, that Pavlov called the "artistic" type, dominated by the "first signalling system," perception, isn't necessarily over-concrete, as Pavlov seemed to imply. The person who uses his body in an integrated way, investing his imagination in important aspects of the real world, can deal with all of the complex and general aspects of society and history, but does it with a sense of purpose, rather than with the Sartrean sense of arbitrary choice. (Sartre's description of the "nausea" associated with this perception gives us a clear sense of the absence of orientation, physically resembling sea-sickness, in the extremely detached form of perception.)

The body and the "older" parts of the brain give precise shape to one's life, and the cortex helps to expand the possibilities that are open to that life.

Apparently, as Pavlov said, the cortex can inhibit the lower parts of the brain, so that the body's own life doesn't enter the life of thought and communication. But the cortex is activated by processes in lower or older parts of the brain, so that it functions with the greatest energy and intensity when it is openly collaborating with the instincts.

For centuries in western countries there has been an awareness of two very different kinds of sexuality. Sometimes these have been identified as "sensual copulation" and "Courtly Love," or as irresponsible and dutiful sexual relations. This double attitude has occasionally been criticized, but it continues in the present culture to serve as the frame for much of the thinking and talking and political activity related to sex.

William Blake was one of the first people who clearly described a kind of being which is whole, or at least trying to be whole in opposition to the culture of doubleness.

"Thou hast a lap full of seed,
And this is a fine country.
Why dost thou not cast thy seed
And live in it merrily?

Shall I cast it on the sand
And turn it into fruitful land?
For on no other ground
Can I sow my seed
Without tearing up
Some stinking weed."

"Sand" apparently refers to a barren emotional state, which is an alternative to a distorted and complex growth of the emotions. Blake often referred to biblical ideas, but

filled with reality and imagination things which had been only the moralistic thoughts of tribal priests--so this verse might relate to the injunction to "spill your seed on a woman's belly rather than on the ground," or something of the sort. Masturbation then would be one meaning of sand--and since in masturbation the energy flow is only in one direction, without exchange and complexification, the idea extends to include this kind of low-energy release in normal copulation. The "stinking weed" is a negation (not a "contrary") of this: A moralistic denial of sex for pleasure. (And of course the thicket of emotional and ideological problems which accompany that attitude.) So Blake presents this unpleasant choice, with an indication that there is something better, a "fruitful land." His whole work contains the belief that sexual energy must be expressed in imaginative fullness, with regard to all of human existence.

Wilhelm Reich, who broke away from the psychoanalytic movement because of his marxian beliefs and his "sex-politics," tried to analyze sexual repression in a biological way. His analysis was the same as Blake's: Both of the culture's sexual alternatives are the result of "armoring," or rigidifying, of the organism. He said that "four-lettering" is not the same as making love, but that it is accepted by the repressive society because it is passive, and less dangerous than full sexuality.

For several decades in the U.S. and Europe there has been a lot of interest in "relaxation therapy," "positive thinking," and other ways of avoiding "tension." Zen and various anti-sexual religions have more recently been grafted onto our own anti-sexual Christian culture. "If there is no adequate way to discharge tension, then don't allow the tension to develop," is their principle.

Stated in terms of the brain's cortex and the older "activating" system of the brain stem, this doctrine would

be: "Let the mind/cortex deal with reality, and the body/reflexes will take care of sex." Too often, what this means is that the cortex and language just have the function of being a short-circuit between bodies. Apparently this is what Blake meant when he said

> "Never seek to tell thy love
> Love that never told can be;
> For the gentle wind does move
> Silently, invisibly."

The mechanical aspects of sexual excitation--genital friction, etc.--are the usual subject of the "neurophysiology of sex." Presumably, sensory nerves in the genitals contribute to increased tension in the autonomic nervous system, including the nerves of the pelvic ganglion. Whatever brainlike quality these visceral ganglia may have, they are still deeply integrated with the central nervous system and the cortex. One general kind of integration is the "setting" of the level at which reflex activity will occur. This control is probably exerted by a balance of excitatory and inhibitory neurons, and by the rate of stimulation, and by chemical influences. The dreaming (rapid eye movement) phase of sleep is apparently a time of great trophic influences of the brain on the body, and it is likely that similar activation of the imagination during the waking state also has an activating and trophic influence on the various tissues. The setting of reflexes and thresholds must be a complex process, relating to the whole life of the organism. If the local sexual autonomic nerves are isolated from the stabilizing influences of the brain, the orgasm reflex can probably occur almost without sensation--a "genital" or "pelvic orgasm" may be little more than a mild peristaltic movement of the tubular muscles. But as the imagination

acts as a "capacitor" or reservoir by preserving tension until the entire personality experiences "resolution" and satisfaction, then the tension can spread throughout the autonomic nervous system, and produce an intensely pleasurable discharge throughout the body, possibly involving some "pleasure center" in the brain. Another way of thinking of tension, besides "reflex setting" and ganglion stabilizing, but describing the same process, is this: The autonomic system tends to maintain balance between its two sides, sympathetic and parasympathetic; if one side is stimulated so its activity increases, the other side increases its tone, to maintain an approximate functional balance in the innervated system. (The quickness and appropriateness of emotional response probably relates partly to the residual "tone" of the autonomic system. This is a factor in "types" of nervous system.) The image would be that of alternately lengthening the legs of stilts--if they are in balance, you can go very high. Some Reichians think of this process as a basis for pathology, not health. But as long as the tension is responsive, and the organism can achieve resolution and discharge, it is obviously not pathological.

The balance isn't invisible and exact--physiological changes occur in the process. The "Effect of Person," which exists not only in people and dogs as a slowing of heart rate (bradycardia), but even in lower organisms as an electrophysiological response, is such a physiological change toward parasympathetic arousal, and during orgasm the bradycardia suddenly becomes extreme--the rhythm changes so suddenly that the heart seems to have stopped. The explanation for this continuity, from "Effect of Person" to orgasm, seems to be that excitement and desire exist as a tension of approximated balance, and that with resolution, the "expectancy" tension of the sympathetic system falls away, leaving parasympathetic dominance. The para-

sympathetic dominance is very similar to the vegetative state of sleep. Cortical resolution, with inhibition replacing excitation, is probably another aspect of this process.

Two things are implied by this analysis: That we can by-pass the cortex if we can't stand the tension (two ways are common in our dichotomous culture--"let's get married," and "let's fuck"), and that if we choose the way of tension we find that our character, our whole way of being in the world, is involved in the way we accumulate and distribute and discharge tension. We find that we will take in perceptions and attitudes from the one we are loving, exchanging perspectives and worlds and bodies. As the personality experiences resolution, we find that our world changes. (Loving intensely is thus a form of objective scientific research--getting new knowledge about the world.) Once we see the interaction of tension and growth, desire and discovery, we realize that sex and imagination are deeply involved in what we can be--that our human existence is expandable and shrinkable.

Just as the brain stimulates and maintains the other tissues, and each hemisphere has a trophic, stimulating effect on the other, the older, instinctive systems of the brain activate the cortex, and exert a trophic, growth-promoting influence on it. Wild animals have larger brains than caged ones, which implies that life and freedom are brain stimulants. Problems are opportunities. People can be the richest kind of opportunity, the most stimulating kind of problem. To do this they have to arouse tension. (Blake said "opposition is true friendship.") This is not to advocate competition. Competition tries to eliminate the problem by defeating an opponent, and can exist only in the armored character, which allows energy to flow only in one direction, and which can't tolerate tension. (An

opponent-friend is one who "inspires" you, who makes you gasp for breath and resolution.)

Pavlov emphasized that the cortex always participates in awareness and behavior, so that the various biological activities of the organism will be oriented with relation to the world; according to his perspective, Reich's "armored" character would probably be considered a variety of hysteria, with cortical weakness, especially weakness of the inhibitory-trophic processes. Muscular tension, for example, increases when the cortex is removed. Where many Reichians consider tension of muscles to be an active inhibition of natural energy flow, the problem might be a failure of brain activity to *actively* relax them, as in the "rapid eye movement" phase of sleep. This relaxation probably results from processes that occur in both the waking and the sleeping cortex.

In spite of the emphasis on the cortex, sub-cortical structures are recognized by the Russians to have many generalized functions (besides serving to activate the cortex, produce dreams, etc.) The autonomic system, for example, is believed to be largely responsible for trophic, regenerative processes. Immunological memory is a particularly interesting case, in which all levels of evolution seem to coexist and collaborate. Even plants can be hypersensitized, and have antibody-like substances (hemaglutinins, etc.), as do various primitive animals which have no white blood cells or lymphocytes, and this same kind of tissue sensitivity seems to coexist in higher animals with the specialized immune systems. The cellular immune response can be modified through the nervous system, and the conditioned reflexes can be formed for specific antibody responses. I. P. Ashmarin (Zh. Evol. Biokhimii i Fiziologii, No. 3, pp. 2170224, 1973) has suggested that neurological memory is built on immunological memory, which is built on hereditary

memory. These other levels of memory, control, responsiveness, have to be kept in mind while considering the cortex: The cortex participates in all of these processes, but each level has its own life and contributes to the other levels. The coordination of these levels is health.

American Behaviorism has given to the phrase "conditioned reflex" a connotation of "involuntary, unconscious behavior which is built up by repetition." In Pavlov's use of the phrase, though, there was no such implication. In his usage, this brain function can be instantaneous and insightful. His purpose was to explain the way we are. Too many American Behaviorists deliberately leave an unexplained residue (creativity, single-trial learning, sudden insight, Gestalt formation, etc.) which has to be filled by dualistic constructions, magical processes, or Kantian limitations to allowable, possible, knowledge. Pavlov (February 6, 1935) discussed this aspect of Sherrington:

> "Sherrington himself investigated the reflex activity of the spinal cord, but he is decidedly against attributing this activity to the higher parts, to the brain; in the latter case this structure becomes in their eyes hypothetical.
>
> This is animist reasoning. Sherrington has built a nest of animism. This is proved by the fact that he doubts whether the mind has any relation to the nervous system. Hence the mind is something beyond and above the nervous system, something that can be detached from the nervous activity altogether.
>
> I can understand the influence usually exerted by a teacher on his pupils. But must all the pupils necessarily be animists if their teacher is an

> animist? Is there really such intellectual serfdom among Englishmen?"

A typical Anglo-American follower of Sherrington is G. Hoyle; he illustrates the persistence of this dualism. While pithing a croaking, struggling frog in a neurophysiology lab, he said "we can't know that a frog experiences pain, because he can't speak to us." And, having the illusion that I was a psychology major, he repeatedly asked whether I was going to study "the nervous system, or the mind?"

Pavlov spoke of a "Reflex of Purpose" and a "Reflex of Freedom." He was aware of the political significance of psychological theories. He claimed we have a real, biological need to be free and purposive. This is utterly opposed to arguments such as Skinner's in *Beyond Freedom and Dignity*. Skinner's claim that we have no instinctive desires is needed to justify the friendly fascism that he advocated. (Usually, the people who argue that we have no good instinctive urges--such as sex--are the same people who argue that aggression is innate: Our culture still teaches about sexless Eden and Original Sin.)

Part of the world of stimuli is internal, within the body, even within the nervous system (spontaneous activity of neurons). Considering the cortex as the mediator between inside and out, we see the internal energies and forms expanding outward, through the brain and through the eyes and other senses, and interacting with the forms and processes of the world.

This general scheme was proposed in the 18th century by Blake, who was the first person to really incorporate biology into a vision of the world. There was much more biological information available in the 18th century than we usually realize, since people like

Swedenborg, Buffon, Lamarck, and Erasmus Darwin, whose ideas were suppressed by their contemporary bigots, are still unfairly treated by our contemporary bigots, who have falsified our historical picture of 18th century biology. Blake described several degrees of consciousness, which we can now see were degrees of cortical isolation from or integration with the rest of the body--ways of being which admit energy and desire to varying degrees.

"Single vision" was his term for the abstracted science of the Newtonians, who said that only extension and mass were real, classifying everything else as "secondary qualities." "In a year of dearth," Blake said, referring to this mental poverty, "bring out weight, measure, and number." Time and space are reduced to series of "infinitesimals," to facilitate calculation.

Ordinary practical consciousness, in which colors are experienced, but only passively or for utility, he called twofold vision. Dream vision, in which the intrinsic beauty of being is enjoyed as images are constructed, was threefold vision. But one's own responsibility for being and imagining and knowing is not recognized in this state, so it is somewhat delusive--typically, this state evaporates as we try to participate actively in it ("The Crystal Cabinet," for example). In fourfold vision, the person recognizes his own active perceptual process, and also sees this active perceptual "humanness" as an objective property of the world. The split between subjective and objective doesn't exist; there is a kind of full resonance between self and world. Blake saw a failure of self-love, a failure of energy, as one of the things that can lead to dominance of the rationalizing process (which leads to "Newton's sleep"). With self-love, there needn't be any conflict between desire and possession; without it, the self shrivels and begins to analyze the object of desire, destroying it. The self is a

time-spanner, unifying past, present, and future. Blake affirmed that, while there is a "limit to contraction, there is no limit to expansion." Analysis is limited, energetic life is unlimited. In this view, sexual love is an ultimate affirmation of self, other, and world.

CHAPTER 7
GROUP ENERGY

> Everything possible to be believed
> is an image of truth.
>
> W. Blake

Until our most exciting discoveries can be fully integrated and taken as a part of our background, we can't advance beyond them. The have to alter our perspectives by taking their place in our cultural framework.

At the present primitive-tyrannical state of mass communication, this emotional-energetic aspect of discovery would limit us to only a little progress in a life-time, if we had only the large culture of civilization. The sexual pair, and other personal groupings, are where culture and discovery really exist.

If our brain is really sexual in its optimal functioning, then we should work out the implications of this: That knowing is for others. If everything is known by forming a dominant for it (personal gesture, object gesture, etc.), then knowing is for the world, knowledge is responsibility.

Somehow, people manage to think of knowledge as being quantifiable, as if it weren't a whole. The normal animal function is to integrate each perception into its world, so that every observation or communication leads to increased generalization.

When an individual enters a group with a loving expectancy, the nature of the group is changed, expanded. The world known by each person is extended. (It's analogous to adding a section to the perimeter of a circle: The angle of the curve is opened with each addition.) Any little perception that is given is likely to come back better.

When another person understands your perception, its truth is evaluated. ("Truth can never be told so as to be understood, and not be believed.")

When a person uses my perception, they are thinking with my mind, and this allows me to advance, energizes my advance. Their new and appropriate way of using it expands my perceptions and my possibilities. Does it feel like this to others when I feel myself "thinking with their mind"?

The belief that reality is a closed system goes with the belief that we can advance only by hindering someone else. Just as "entropy increases in a closed system," such an ethic tends to spread shrinking withdrawal and hostility. Doing something from a social motivation seems to detract from its intrinsic goodness, according to this view. Doubt, quantifiable knowledge, knowing as discrimination rather than as synthesis, are functions of a shrinking self, absorbing energy. But the expansive pursuit of knowledge is one of the strongest social bonds, because we *perceive* others as vital parts of our selves.

Metabolic energy can illuminate patterns in the world, generalities. These new perceptions will liberate metabolic energy when taken up by another person, so that communication is energizing..

When you let yourself get highly energized, your sense of energy expenditure increases, your sense of the importance of certain things increases. This is what draws a real group outside of itself. Every perception is seen to have relevance to the world. Everything comes to be done with involvement and wholeness. To the person who passively belongs to the culture, it looks as if everything has become difficult for the involved ones, and this seems inefficient. But to the productive group, it looks as if everything has become possible.

CHAPTER 8
SCROTUM, BRAIN, AND BIOLOGICAL ORDER

A friend asked me this interesting question: "Why do higher mammals have to keep their testicles cool, while birds can produce active healthy sperms with internal testes and very high body temperatures? What advantage is it that's worth the risk of losing them by snagging on a branch, etc.?"

After expressing my ignorance, I thought for a minute with this result:

Racist geneticists to the contrary, there is no evidence that either intelligence or brain size is genetically inherited, since acquired changes are heritable, and since only one protein peculiar to the brain is known, at present. Other brain-specific proteins will probably be discovered, but despite a large effort in that direction, there is no hint of a molecular-genetic basis for "inherited intelligence." Glucose, hormones, stimulation and other factors significantly modify brain size and function.

The electrical gradient which exists in the adult organism--brain, head and back, positive, liver, belly, and extremities, negative--exists already in the egg--animal pole positive, vegetal pole negative. Ion selectivity corresponds to cell electrical potential (and to cell longevity or stability), and is probably determined by the orderliness of cell water (Szent-Gyorgyi, Wiggins).

Environmental ion concentrations can modify the normal developmental gradient, resulting in vegetalization or animalization. This very likely reflects ionic influence on the orderliness of the water-protein system. If the structure

can modify ion concentration then ion concentrations can undoubtedly modify the structure.

Sonneborn coined the word "macrocrystallinity" to describe the cytoplasmic inheritance he observed in paramecia. The developmental gradient of potential and structure suggests that "microcrystallinity" is also an aspect of cytoplasmic inheritance. Accumulated biological stability, or wisdom would be reflected as high orderliness, high ion selectivity, high electrical potential, and high efficiency of energy metabolism--in the "animal pole," and in the brain (and in the intermediate developmental stages).

As molecular disorder tends to increase at higher temperature, order tends to increase at lower temperature, and this is especially important in water near proteins or other surfaces.

If gamete formation involves the creation of cytoplasmic order as part of the instructions of development, lower temperature at crucial times would facilitate the creation of a high gradient.

If brain evolution--which is so spectacular in mammals--is a product of the developmental gradient, then cooling the gametes as the cytoplasm is structured would facilitate the inheritance of larger brains.

If a large brain, through an electronic, metabolic, or temperature gradient, can increase the structuring process of the "animal pole," it would account for the observed inheritability of brain changes caused by diet (or stimulation).

Weak ultraviolet irradiation of frogs' eggs produces anencephalic or small brained tadpoles (Grant). Irradiation of women, especially in early stages of pregnancy, by atomic bombs in Japan, produced a high proportion of small brained children. If there were many genes for specifying the development of brain, relative to the number of genes

for all other tissues, mere gene mutations might explain this effect of radiation--the tissue that depends on the largest number of genes would be the most sensitive to radiation damage. The liver, with a greater variety of enzymes than other tissues, would seem to be the most subject to gene damage, but there are no stories of liverless fetuses resulting from radiation damage.

Radiation does disrupt water structure, and stabilizing water structure protects against radiation damage (Webb). Excited electronic states--e.g., singlet oxygen--are known to last longer in cell-water than in bulk water. Solvated electrons also have a special stability in cell-water. The interactions between water and radiation are of great importance, but much more research needs to be done in this area.

It seems more reasonable to interpret the effect of irradiation on brain development as a melting of the water structure that supports the developmental gradient, than to suppose it is a gene effect. Not only do we see that the brain is highly susceptible to ionizing radiation, without any apparent genetic reason, but the brain and the gonads are the most sensitive to non-ionizing electromagnetic fields, according to Yuri Holodov. (After I spoke with Holodov, I placed a magnet near a nerve preparation, and found that the nerve's latent period was extended, as if the resting state were stabilized by the increased magnetic field.)

The scrotum would thus be partly responsible for the mammalian advantage over birds in brain development. The sperm might have more influence than its small size would suggest, by a crystallization process similar to touching a drop of super-cooled water with a tiny ice crystal. (Earlier in this century, unfertilized eggs were made to develop "parthenogenetically" by chilling them or by touching them with a needle.)

The "estrogen surge" around the time of ovulation might promote a similar ordering process in the unfertilized egg by causing a drop in temperature. Progesterone is "thermogenic," and increased estrogen seems to counteract progesterone and lower body temperature. (However, estrogen itself seems to cause cytoplasmic "melting"--Nemetschek-Gannsler--for which lower temperature might merely be compensation.) The fact that progesterone is involved in activation of the developing ovum, and that it sets the body's "thermostat" higher, suggests that it in itself introduces a kind of "crystallinity" into the cell-water. (I have discussed some of the implications of this elsewhere, e.g., in Physiological Chemistry and Physics, and evidence is accumulating supporting an important role for progesterone in brain development.)

Old people tend to have lower body temperature, and this might be another case of the body's attempting to increase order in the water-protein system (against disruptive influences of age), in a sort of hibernation reaction.

The gonad temperature of large-brained cetaceans would be an interesting test of the generality of this idea: Are they located in a cool area of fat? Does the cool ocean water offer them even greater protection than the scrotum of land animals?

CHAPTER 9
A VISUAL SCANNING SYSTEM AND INTENTIONALITY

In the time since 1956, when I started exploring visions and my visual apparatus, I have found that people with philosophical or scientific "training" are often very intent on telling others what they "can't" see, or mean, or experience. As a result, I have been concerned with the real experiential differences that underlie differences of world-view, values, and attitudes. I think it's proper to refer to these as physiological differences, since the body is obviously doing profoundly different things when it creates new knowledge, and when it enforces old knowledge against the new, etc.

Part of Maslow's definition of the self-actualizing person was the ability to perceive truthfully. Reich called truth "a natural function," "an integral part of the organism," and "a function most akin to growth." The form of the act of perception will vary in a systematic way with the form of the perceived world, reinforcing or expanding the particular world-view.

There is often a prejudice against vision, in favor of muscle perception, but vision is just as much a body function as is muscular activity, and it has the advantage of involving the largest group of sensory nerve fibers, and of being more richly spatial than other senses. "Primary perception" has visual aspects that can allow very subtle but clear understanding of the living interaction of body and world.

One pole of perception and world-view is represented by surrealists, non-Hegelian marxists (this is an

important distinction, since academic marxists in the U.S. are hard to distinguish from Hegelians) and phenomenologists, and another pole by structuralists, mechanists, and idealists of a Cartesian or Platonic sort.

Surrealists are, among other things, people who can sense their own nerves, and so are better phenomenologists than Husserl, who thought bracketing or purifying experience yielded essences, Platonic forms on which to build a firmer science.

The surrealist experience yields intentionality itself, and the various biological interfaces with matter, or "surfaces" (e.g., nerve endings, or dream substance), as well.

Establishment scientists act as though they had received Husserlian forms on which to build their mathematized "final solution" to the problem of reality.

Surrealist and evolutionary science must talk about a different reality, because fluid *people* can experience fluid *material*, a finer and faster and more fluid perceptual world. Any real "*epoche*" (bracketing of the experiential) will reveal the perceptual functions of the body and its interactions with the world.

Visual "streaming," which varies in coarseness with different conditions, is something anyone can see and explore, but even intelligent people can dismiss it as "only subjective" or "only blood corpuscles." The fine-grain activity that constitutes ordinary vision is over-looked by nearly everyone: Attending to the object, instead of their perception of it, they may experience the *limit* of visual acuity, but only rarely do they *see* their visual acuity, as responsive points.

In bright sunlight, looking at the sky, white discs zoom around--A. Einstein and others have decided they must be "blood corpuscles," but they can be made to zoom

in ways that corpuscles couldn't. Closing one eye will reveal their continuity with the streaming, dust-like particles: High energy stimulation just causes local "explosions" to stand out.

Staring at a radial (or other repetitive) design will set up intense movements in the "retinal dots" that persist for several seconds on a blank surface, or with the eyes closed--this is a way to learn to attend to the dots. (Or by attending to the closed right eye, while holding the design in front of the open left eye.)

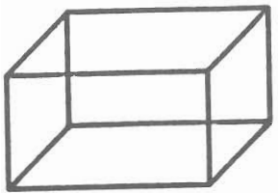
Since the dots are so much smaller than the fovea, the normal area of "concentrated attention" (whose exact form can be seen by "swinging" the eyes freely in the dark, with a light source illuminating the interior of the eye), it at first seems absurd to try to catch a single point with the attention. Making the effort, though, you discover that this fine but intense effort will make a point "explode" in a blue flash, or extend itself into a "fluorescent" needle or sheet.

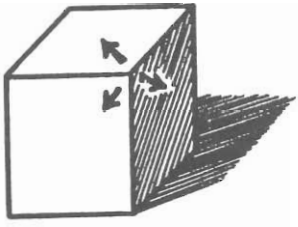
This results from an intensification of the normal antidromic "renewing" activity of the optic nerve. With practice, or with outside stimulation from flickering lights, you can project foveal, or peri-foveal, movies in vivid color.

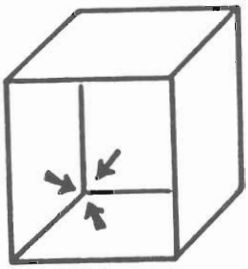
The experience of "after-motion" in reverse, when a car in which you are riding stops after a period of continuous motion, reveals that motion and apparent size (the swelling or shrinking of the landscape as it seems to move toward or away from you) are produced by the "intentionality" of moving dot systems.

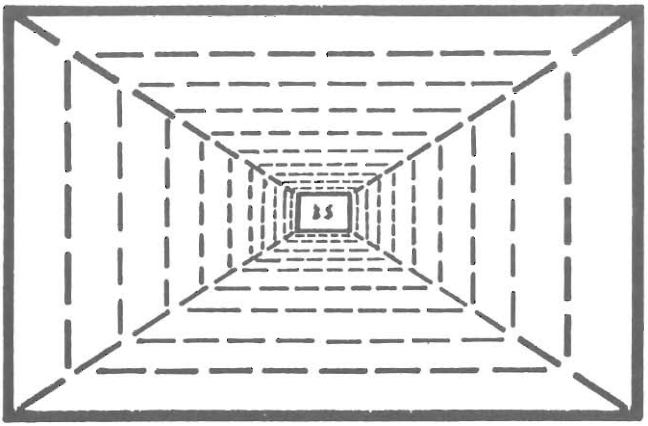
The altered apparent size of an object when it is interpreted as near or far is at least partly governed by this system, as can be seen from an image such as this triangle in the accompanying figure.

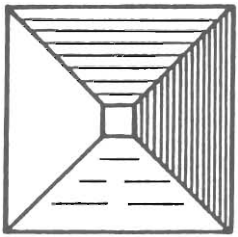
In the triangle, parallel lines seem to swell and diverge when the top is forced perceptually to recede, and

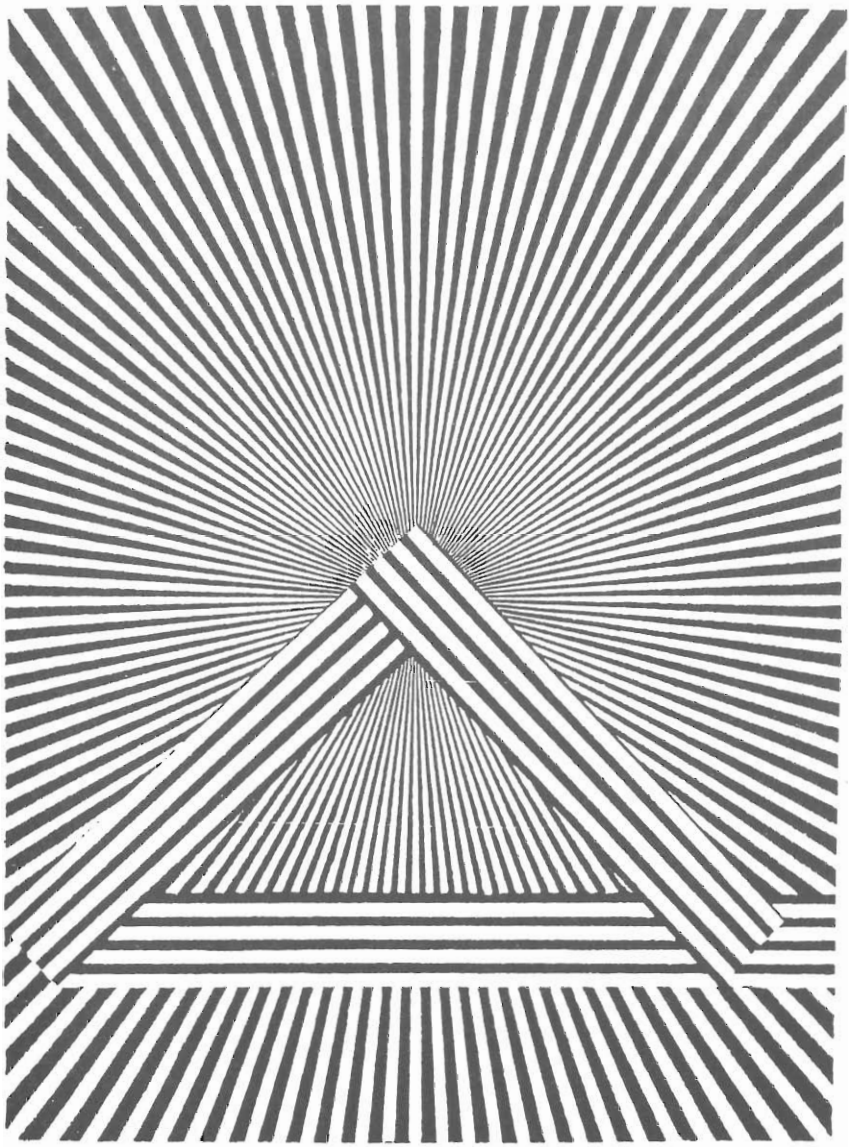












the scanning flow can be seen to become centripetal, with the intentional projection of depth. In the same manner, creating very near space, or "intending" a space very close to the eye, will case a centrifugal flow from that area.

The cube which can be intentionally reversed, in the accompanying figure, is a very clear way to observe that your projected space is the cause of very "appropriate" retinal streamings. The directions of the flow are shown in adjacent cubes with arrows.

I remember that either Michael Polanyi or Merleau-Ponty wrote that we may not be able to perceive the "neural response" which underlies a perception, but here is a case where that kind of "complete" perception is possible.

J. H. Fremlin (*Nature 238*, 406, 1972) has made an observation (a sensation of structure being built up by staring at flowing water) that suggests how movement of the scanning system can lead to the perception of space, though it doesn't imply that other processes--more internal--may not produce movement in response to projected space. Visual cortex processes probably project a space, which governs and interprets the streaming surface. This is what feels like the "pusher" of energy into the eye, and it's the grainless, dream substance--in Dali's terms, the Camembert cheese, behind the caviar.

The visual "tunnel" that often appears with flickering lights, as illustrated diagrammatically by the rectangles with diagonals representing corners, corresponds to a scanning similar to sand going down a rat-hole. That is, mere external stimulation generates space, depth--or at least the excitement promotes that tendency in our perception.

The scanner *follows* a moving pattern, expanding when it expands, spinning clockwise when the pattern spins clockwise, etc. Since a distant image causes shrinking, it is

as though the scanner is "catching" the scene, preventing the "recession," and magnifying it or evening out the apparent size differences caused by angle.

The "inner" intentional space encompasses the body and generates the space in which objects of other senses can be located--some auditory fibers, for example, travel into the visual cortex, as if sounds were to be perceived visually to a certain extent. In dream states, with body input blocked, ordinary perspectives aren't necessary--depth can be experienced without direct reference to the eyes.

Something very similar to Fremlin's observation can be easily visualized with a regular object or image--that is, a symmetrical image, with one-sided illumination, that can be viewed as either concave or convex, with light imagined as coming from one direction or another. The line-cube shows the same process, though less concretely, since no textures are involved. Viewing a figure like that in the illustration ("pyramid") it is harder to see it as a flat design, and it will bulge or recede, depending on where you imagine the light source to be. This is a familiar problem in interpreting photographs of microscopic crystals, etc. The real perception of form and depth, without either movement or binocular vision, reveals that space perception is inherent in consciousness, even without the *constructive* processes of motion or two-eye vision. The "retinal streaming" that accompanies this space peception reveals a physiological aspect of intentionality. These observations allow us to avoid the idealist-abstract identification of intentionality with symbolization, and the mechanistic assumption that it is only gross body geometry which makes it possible. The behaviorists used to say that our bodily kinesthetic sence provided the space for organizing our vision, and more recent views have implied that it was the intrinsic triangulation of binocularity which creates our visual space.

I want to suggest that a kind of "space filling" brain process is an important factor, in addition to the other bodily "space filling" events. Such an inner space, resonating with the outer spaces, can be thought of as a tissue hologram.

Once the visual steaming is perceived, the "mechanics" of all the familiar optical illusions of line, space, movement and size distortion become intuitively obvious: The rosette illusion, bulging circle, big moon on the horizon, non-parallel lines, etc., all are simple interactions between the scanning stream and the object.

Much more important than explaining illusions is the effect that contact with visual streaming has on our interpretation of the world: If a mechanistic-symbolic idealizer of space (like the psychologists who publish abstract "explanations" of illusions, for example) is tricked into experiencing his own perceptual system, his experience of fluorescent consciousness is likely to give him a new respect for all matter. Blake frequently described the new attitudes that come with altered perceptions, for example, "Over sea, over Land/ My eyes did Expand.... In particles bright/ The jewels of Light/ Distinct shone & clear./ Amaz'd & in fear/ I each particle gazed,/ Astonish'd, Amazed; For each was a Man/ Human-form'd. ...My eyes more and more/ Like a Sea without shore/ Continue Expanding...."

CHAPTER 10
INHIBITION AND RECUPERATION

Inhibition has a bad name in America. The common understanding of the term grows out of popular Freudianism: e.g., libidinous urges must (or must not) be inhibited--that is, energies are rigidly instinctual, and can only be deformed by operating within a social framework. In Russian thinking, however, inhibition has both a general organismic meaning, and a cellular meaning, which have nothing to do with the popular meaning of the word. In Anglo-American neurology, cellular inhibition is generally believed to be a matter of specialized inhibitory nerves and inhibitory substances, while in the Russian tradition the tendency is to think of it in a more generalized way, as something that can be applied to any cell, nervous or otherwise. This difference leads to some therapeutic and preventive approaches in Russia that seem unscientific in the West.

Sechenov, the "father of Russian physiology," was the first to observe nerve cell inhibition: he found that a frog's spinal reflexes, such as kicking, could be suppressed by intense stimulation of the sensory nerves. Vvedensky then found that an individual nerve became inhibited if stimulation were too intense or too frequent, and that this was not mere fatigue, since it could begin functioning immediately under weaker stimulation. Pavlov found many conditions in which a particular behavior could be inhibited, and also noticed that the entire nervous system could go into an inhibited state. He discovered that inhibition is not an inactive state, but that the cell is cut off from stimuli, and undergoes a process of restoration. During excitation, there

is a build-up of ammonia, lactic acid, and inorganic phosphate within and around the nerve cell, as well as a depletion of energy reserve and even a change in the condition of the cell proteins themselves. (E.g., Berestovskiy, G.N., et al., "Study of the cumulative structural changes in a nerve fiber during rhythmic stimulation using optical techniques," Tsitologiya 14(12), 1461-67, 1972.) Pavlov suggested that psychosis may be a state in which the nervous system goes into partial inhibition to restore itself, and prevent complete exhaustion and death. Recently in England and the United States, R. D. Laing has proposed the same idea: that insanity is potentially a recuperative process, if we don't punish patients with our treatments. An obvious approach to treatment--from the Russian point of view--is to help the patient regain his nervous "energy potential." Nutrition, rest, and even direct supplementation of the high energy substances are possible approaches. Certain kinds of weak stimulation can also be used to reinforce the inhibition and promote sleep.

This use of weak stimulation to promote inhibition is particularly interesting, and related studies are being done by a few people in the West. Recalling the idea that an organism "selects an environment" to which it can respond during its evolutionary development in the world, we can see that there will be an infinity of events both "above" and "below" the part of the environment used by the organism, and that just as the organism uses inhibition to protect itself from excessively strong stimuli which would destroy it, it can use inhibition to avoid the endless fatigue of being alert to irrelevant and "small" stimuli. Normally, this inhibition seems to be very flexible: we can learn to concentrate on different kinds of things, and we can shift our attention and instantaneously change our pattern of inhibitions. Some psychoses apparently involve a failure of this kind of

inhibition, and it has been suggested that abnormal behavior may be an indirect way of defending oneself against excessive stimulation (e.g., Hoffer). This need for selectivity is apparently what accounts for the development of a system in which weak stimulation promotes inhibition. The kind of inhibition produced by weak stimuli is very different from that produced by excessive excitation: it represents a state of heightened (rather than impaired) readiness.

We can think of two zones of inhibition, separated by a state of activity: The "lower" zone somewhat resembles lower forms of life, and borders on death (the "parabiotic" state), while the higher zone of inhibition is a highly structured state with higher energy reserves even than the active state--it is a state of "high readiness." (There may be another active state between "lower inhibition" and death, since exhausted and unconscious people and animals frequently regain consciousness briefly just before dying.)

The various states of the nerve cell can be appropriately thought of as different degrees of "tightness" of the protein gel structure of the cell substance. Mild mechanical or chemical stimulation (e.g., small doses of caffeine) will inhibit the nerve tissue, and in doing so will make the cells impermeable to penetration by foreign substances such as dyes, and will improve their resistance to oxygen deprivation. On the other hand, excessive stimulation increases their permeability to dyes. The so-called "blood-brain barrier" is an illustration of this resistance to foreign materials by cells in their normal "tight" condition.

Extending the hours of sleep each day (for example, with a mixture of soporific drugs) can almost cut in half the time required to recover reflex functions after spinal damage (Asratyan and Simonov). Sleep, a state of extensive

inhibition, apparently accelerates the cells' recovery of their energy reserves.

By controlling our perceptions, selective inhibition is obviously participating in the control of our behavior. Just as concentration is necessary for clear perceptions, patterned inhibition is necessary for controlled behavior. The discovery that coffee (or amphetamines) will control hyperactivity in children seems to relate to caffeine's ability to produce inhibition, as well as excitation--the effect depends both on the dose and the prior state of the tissue.

Examining our experience, we can see some of the interesting aspects of inhibition--these processes are things we can feel and see, not just a mysterious something happening in a mysterious somewhere. When we close our eyes, the level of blackness we see is one indication of the amount of "readiness" or primary inhibition in our visual system. Without good visual blackness, we are analogous to a fogged photographic film: We lack contrast and vividness, unless the highlights can somehow be made brighter. When we are ready to go to sleep, and primary inhibition is setting in, our visual blacks are very pure, and we see very clear "hypnagogic visions." If we go too long without sleep, this clarity is replaced by a buzzing confusion and an unsatisfying kind of half-sleep: We have apparently built up the low-energy condition in our nerve cells to the point that our primary inhibition is defective. Continued too long, brain activity will pass into the inhibition of exhaustion.

Sleep, by restoring the "high energy" state of readiness, affects all the tissues of the body through the effects of the nervous system. Many people who have migraine headaches, for example, have discovered that just a few moments of sleep--just drifting into the dreamy forgetful state--can interrupt the regular progression of

symptoms, if it comes before the pain is so intense that it make sleep impossible. Some women have discovered that a short nap can interrupt their monthly cramps. Since the "cause" of menstruation is the disappearance of progesterone while estrogen is still at a high level, these cramps can probably be attributed to estrogen's promotion of an excited state in the cells of the uterus, equivalent to the epileptic seizures that can be produced by higher quantities in the brain. Exactly how sleep and its state of primary inhibition can manage to offset the uncontrolled activity of cramping muscles isn't clear: It might be a direct inhibitory effect of nerves, or an indirect effect such as an increased concentration of blood sugar.

The fact that women have migraine much more often than men, and that it is usually related to the menstrual cycle, suggests that an estrogen imbalance may be involved some way in migraine, which makes the effect of sleep on both cramps and migraine especially interesting. Migraine is often considered to be an uncontrolled dilation of blood vessels in the head (very much like hemorrhoids except for the location) possibly resulting from depletion of a substance which constricts vessels. Blood sugar also seems to be low in migraine, so that some people find that eating a large amount of ice cream can interrupt the symptoms. This observation might be what we need to understand the role of sleep in health. We all know how hard it is to sleep when we are hungry (low blood sugar), and how sleepy we sometimes get after a big meal. Low sugar levels in the blood can literally starve some cells into malfunctioning: This is how insulin shock causes convulsions and hallucinations. The hallucinations that occur in cancer may also indicate cell starvation. (Shapot, et al., have demonstrated that cancer always disturbs sugar metabolism.) Usually, a cell emergency will cause

surrounding blood vessels to dilate, to allow more blood to be delivered to meet its needs. The adaptive release of transmitter substances is probably part of this process, and increased production of carbon dioxide and lactic acid will cause the vessels to dilate locally. Additionally, mere exhaustion from sugar-starvation is a factor in causing the blood vessel muscles to go slack and cause localized symptoms. How would estrogen be involved in this kind of process? Something I noticed in my work with hamsters may be relevant: Estrogen in excess causes wastage of both oxygen and sugar. If sleep inhibition can merely restore enough stability somewhere in the body that the wastage becomes manageable, adequate cell nutrition would again become possible. Since "migrainoid" people typically have very high levels of brain electrical activity, the brain itself might be a significant energy drain. (It has been estimated that the brain uses 25% of the body's energy, and it is almost completely dependent on glucose for its energy.) "Plugging" this drain could cause a sudden rise in blood sugar and other nutrients, allowing the exhausted cells to recover their energy and their stability. A state of "high readiness" seems to be an efficient state, in its use of oxygen and food.

Disturbed intestinal absorption of sugar might also be a factor in this energy problem. And reflexive distribution of tension in the autonomic nervous system is definitely involved. The entire nervous system is "meaningfully" interrelated, so that, for example, stretching of (or pressure on) the rectum will decrease diuresis (urine formation) causing the organism to retain water (N. A. Miasoyedova), and intestinal muscle tone will change, blood pressure will be altered, etc. If the stimulation of an organ (for example, the rectum) is extreme, relative to the resistance of the organism, a pathological condition may

appear, such as a disturbance of heart rhythm. Even epileptiform convulsions can be induced by such stimulation--for example, irritation of nerves in the lungs is a factor in the convulsions produced by breathing excessively high concentrations of oxygen (Chernigovskiy, *Interoceptors*, 1967). This shouldn't be surprising, since it used to be common knowledge that intestinal worms cause dogs to have fits, and caused children to cough--but since penicillin became more popular than worm-medicine, many people seem to have forgotten their folk-wisdom. Even something as simple as inflating a balloon in the stomach can cause changes in the cellular composition of the blood. Obviously, toxic or allergenic materials in the digestive tract will have similar effects. "Allergenic" means anything which irritates by way of the immune system, and will vary according to the excitability of the individual. Excitation is increased when blood sugar is low, and when this state was induced by insulin, it was found that a slight stimulation of the intestine provoked strong, disorganized motor activity in the animal, including asthma-like reactions. Other studies show the same association of blood sugar with allergic reactions.

These are just some samples of the ways inhibition and excitation interact in the organism's behavior and physiology. In the U.S., most thinking about "inhibition" is either on a moralistic and Freudian level (control of impulses), or on the microscopic level of synapses. In Russia, the organism is the central phenomenon, so integrated studies of metabolism, behavior, and environment are the rule. Far from considering the "visceral nervous system" as a nearly autonomous thing, the Soviets have found that the internal organs are "represented" in the cerebral cortex, with both "sensory" and "motor" components. They are less sharply localized in the brain

than are the analyzers of the "external" senses. Since brain localization of the external senses increases with evolution, as a nucleus is developed where increasingly fine discrimination and analysis is performed, we might guess that increasingly fine discrimination of our visceral senses hasn't been desirable--since their functions are fairly standardized, gross coordination might be best.

In my study of estrogen and aging, I found that the effects of excessive estrogen and of aging itself are practically indistinguishable on the level of cells and tissues. If sleep is so effective in blocking the "acute" symptoms of an energy disturbance which is largely attributable to estrogen, what would it do to the energy disturbances which constitute aging? It is generally known that old people sleep less than young people, and it is also known that the old brain tends to be in an "alarm" state, lacking inhibition. Several years ago, some Russian physiologists maintained a 17 year old dog on "electrosleep" with intravenous feeding for six months--because of the toxicity of chemical anaesthetics such a long sleep required the new method. When they wrote their report, the dog was 20 years old but no longer suffered from his former senile condition. This suggests how important sleep and inhibition may be in the various degenerative diseases. A proper balance between excitation and inhibition seems to be a factor in recovery from most diseases.

NOTE TO CHAPTER 10

Nasonov's staining method gives us a key to understanding stress, nerve function, and cell activation in general.

The common Soviet view (evidence reviewed by Troshin) is that the concentration of substances in cells is regulated not by a "cell membrane," but by the adsorptive state of protoplasmic proteins, and by their solubility in the cell water or gel. Through evolution, protoplasm presumably develops a more and more highly refined selectivity. Nerve and skeletal muscle cells have highly variable selectivity for ions, and high sensitivity. In their so-called "resting state," nerve cells have very high selectivity, but this is an equilibrium process--the excluded substances enter and leave the protoplasm at nearly the same rate, rather than merely being excluded by the surface. The "blood-brain" barrier may be an example of such exclusion (Verzhbinskaya). In the "activated" state, nerve cells admit "extracellular" ions, such as sodium, but "recovery" of the exclusive state occurs instantaneously. The state of proteins momentarily resembles denatured proteins. With excessive stimulation, recovery is incomplete and, with the proteins and gel structure in a partly denatured state, foreign molecules (dyes) introduced experimentally can be observed inside the cells.

Szent-Gyorgyi's description of the "staircase" phenomenon (in which the strength of the heart-beat increases with its rate of beating) indicates how a certain amount of stimulation can *maintain* the native structure. The stimulation can apparently be either physical (electricity, etc.) or chemical (caffeine, transmitter substances, digitalis, etc.) He described this as "function building structure." (Isn't it odd that people who advocate exercise think a slow pulse is good, because it allows the heart to work less?)

The effects of stress and stimulation have been studied by Nasonov's dye method, as well as by more conventional biochemical analysis (Palladin). For example, the brain's ATP content was found to increase with evolution and with the degree of alertness.

The fact that small doses of caffeine help in some cases of schizophrenia may be the result of this restorative process of mild stimulation.

This effect of stimulants is probably also involved in their inhibition of cell division in cultured cancer cells (ephedrine and

theophyllin, for example), and the ability of caffeine injected into the brain to retard tumor growth elsewhere in the body (Kavitskii).

Incidentally, this view implies that there are at least two general mechanisms for anesthetics or narcotics--those which block by stabilizing at the high energy level (this group probably includes progesterone) and others which block by preventing recovery.

DMSO apparently introduces some "hydrophobicity" into water, because of its strong hydrogen bonding oxygen and its methyl groups--at least it seems to lower the effective activity of water (Berezin, Ugarova, and Silaev, 1973). This may mimic the resting state of protoplasm to some extent, since it seems to improve metabolic efficiency: Reducing inflammation and treating mental retardation are its best known (apparent) effects. The disappearance of cataracts in the eyes of retarded children is another suggestion of improved oxidative efficiency (dinitrophenol, an uncoupler of oxidative phosphorylation, produces cataracts, as does age, which also involves oxidative inefficiency).

CHAPTER 11
HYPERACTIVITY

The various tissues of the body can function acceptably at different levels of nutrition. For example, the skin, with its low energy requirements, seems to remain alive for many hours after the death of the body in general. The brain, with its extremely high energy requirements, is usually the first to suffer from energy deprivation. At slight levels of deprivation, the brain will simply lose functional efficiency, but more serious or prolonged deprivation can produce lingering modification, or even structural damage which is relatively permanent (and may even have transgenerational effects.[1]

Just as the skin (or muscle) has a lower energy requirement than the brain, the various parts of the brain have different requirements. The parts which are most resistant to damage are the "lowest" and "oldest" parts of the brain, the parts we have in common with frogs. These parts regulate physiological processes, such as breathing, and so it is biologically useful that they should be most resistant to damage. When a person is given an anesthetic, the first parts to stop functioning, or to go to sleep, seem to be just those parts that have the highest energy requirements, and which are least resistant to damage. The anesthetized person keeps breathing, for example, until very high doses of anesthetic are given, but other functions disappear one by one as the dose increases.

The front part of the brain, which is most uniquely human (and "newest") but which doesn't have "specific" function, in the usual sense, is one of the most sensitive parts of the brain. It is a very large piece of tissue, and it seems to be involved in planning and choosing, in governing

the other more specific functions (This part of the brain, as well as the cerebral cortex in general, gives us the ability to "disregard" stimuli, to use Lendon Smith's term.)

The famous Russian neuro-psychologist, A.R. Luria, has described the behavior of dogs when this tissue is damaged or removed:

> ...destruction of the frontal lobes leads, not so much to a disturbance of memory as to a disturbance of the ability to inhibit orienting reflexes to distracting stimuli: ...such an animal cannot perform tasks involving delayed responses under ordinary conditions, but can do so provided that irrelevant, distracting stimuli are removed (if the animal is kept in total darkness, if tranquilizers are administered, and so on).
>
> The role of the prefrontal cortex in the synthesis of systems of stimuli and the creation of a *plan of action* is manifested not only in relation to currently acting stimuli, but also in the formation of active behavior directed towards the future.[2]

Various theories of what causes hyperactivity, e.g., low blood sugar, weak radiation from fluorescent lights and TV,[3] or food additives,[4] and the observation that drugs which stimulate the sympathetic or adrenergic nerves (ephedrine or caffeine, for example) will relieve the symptoms, are all consistent with the idea that not enough energy is being supplied to permit this tissue to function properly. Low blood sugar will starve the nerves; food additives or any low-level poison can serve as a stressor of nerve tissue, leading to increased energy requirements;

many forms of very weak radiation[5] can lower the efficiency of metabolism, increasing the tissue's energy requirement, and brain tissue is the most sensitive to at least some kinds of radiation.

Intestinal irritation can cause disturbances of the nervous system,[6] and should be considered as a possibility in "disorders of attention." Toxins produced by intestinal bacteria can affect the brain directly, but more often act by damaging the liver's ability to regulate blood glucose.

The commonest cause of hypoglycemia is hypothyroidism, and a thyroid deficiency increases the tendency toward a high-adrenaline state, but more importantly, thyroid hormone is the basic regulator of efficient energy production. Memory and attention are impaired by even a slight thyroid deficiency. The Russian paradigm, with its emphasis on energy and inhibition, suggests that thyroid function should be carefully examined in cases of hyperactivity. Too often, western physicians think only about *hyper*thyroidism in hyperactivity.

1. A.E. Needham, *The Growth Process in Animals,* Van Nostrand, Princeton, N. J., 1964.

2. A.R. Luria, *The Working Brain,* Basic Books, N.Y., 1973.

3. J. Ott, *Health and Light,* Devin-Adaire, Old Greenwish, Conn., 1973.

4. B. Feingold, *Why Your Child is Hyperactive,* Random House, N.Y., 1975.

5. A.H. Frey and S.R. Feld, "Avoidance by rats of illumination with low power nonionizing electromagnetic energy,"*J. Compar. and Physiological Psychology 89*(2), 183-188, 1975.

6. V.N. Chernigovskii, *Interoceptors,* American Psychological Association, Washington, 1967.

CHAPTER 12
IMPLIED THERAPEUTIC APPROACHES

The biophysical theory argues that altered consciousness (and the behavior it produces) is a question of both bioenergetics and "bio-microstructure," and implies that a therapy should attempt to create the desirable state of structure and energy by intervention at crucial--and possibly numerous--points.

I don't know whether ATP has ever been used therapeutically for psychosis, but since it is one of the central points in both energy metabolism and structure, its use is definitely suggested by the theory. Of course, creatine phosphate, which is in equilibrium with ATP, might be an alternative way of raising ATP concentration, since it is at a higher energy level and would not introduce additional adenosine, thus allowing a higher ATP/AMP plus ADP ratio, if not an absolutely higher concentration of ATP. ATP has been found to improve the functional state of the brain (vestibular analyser) when used with pyridoxine, increasing its stability and shortening postrotatory nystagmus (Lapayev, et al., 1971) (Also, it promotes healing of corneal wounds at high altitudes, when applied locally with 4-methyluracil, Vovsi, 1972.)

Other "orthomolecules" besides niacin would be potassium, vitamin E (improving oxygen supply, facilitating cell retention of proteins), inositol (stabilizer of cells and proteins against denaturing or "dehydrating" influences, Webb, 1965) the other B vitamins, vitamin C, anabolic steroids (for example, the androgens, and progesterone, ginseng, eleutherococcus) to promote protein synthesis and retention of potassium and creatine and ATP. Progesterone

may be particularly important in female schizophrenics, since it commonly seems to promote emotional stability and even has an anesthetic function in large doses. (Selye, 1967.)

The electronic aspect of the cell's energy charge suggests that cysteine or reduced glutathione might be desirable, especially if there is evidence that glutathione is being destroyed by something like adrenochrome. (Sulfhydryl blocking can impair glycolysis, as can a niacin deficiency.) The theory of donor-acceptor interaction might eventually lead to a specific understanding of the "electronic leak" and how best to intervene, though it might not be such a discrete problem as some theorists have hoped.

The glutathione peroxidase which is released when mitochondria swell might be involved in the "electron leak," and so things which cause uncoupling of oxidative phosphorylation and mitochondrial swelling, such as unsaturated fatty acids (Racker, 1965) should probably be controlled in the diet.

Since the normal person has sharp diurnal cycles of brain activity (reflecting a proper concentration of the "brain" amines) and many psychotics have flattened cycles, involving disturbed sleep as well as disturbed waking consciousness, cyclic light stimulation of skin and head might be desirable to support regular cyclic activity of the pineal gland and brain. This would also tend to increase sex hormone production by the gonads (Kinson and Peat, 1971). The brain's "background activity:" might have what in the heart is called the "staircase" effect, in which structural readiness seems to leak away if the tissue doesn't become active often enough--"function builds structure, and structure produces function" (Szent-Gyorgyi, 1972).

Hyperbaric oxygen therapy has been used in relieving psychotic symptoms (Kondrashchenko, et al.,

1971), but this doesn't seem appropriate for creating lasting improvement. The opposite condition, i.e., high elevation, has caused lasting improvement in psychosis (Mirrakhimov, 1972) and many somatic and psychosomatic conditions, and the mechanism (according to the animal studies of F.Z. Meerson, 1972) is the adaptively increased number and efficiency of mitochondria in the brain, resulting in improved learning ability. Also, MAO activity decreases at high elevation while respiratory effectiveness increases (according to Khvatova, et al., 1973).

The changes Meerson's group has seen in high altitude therapy resemble the changes that occur during supplementation with thyroid and antioxidants. The lower concentration of oxygen in tissues at high elevation would increase the antioxidant reserves of the organism, making it more resistant to stress. Decreasing the use of dietary unsaturated fats similarly protects against oxidative stress. These changes, including thyroid supplementation, increase the proportion of useful oxygen consumption in relation to harmful oxidation of tissues, and increases the useful stores of tissue energy.

Optimizing the production and storage of energy will have the effect of tightening the control systems of the organism, improving mental, hormonal, and immunological functions. These changes are probably involved in the greater effectiveness of cancer therapies at high altitude.

In a pharmacological approach, reduced expenditure of glycogen, ATP and creatine phosphate (Dardymov, 1971) combined with increased protein synthesis (Rozin, 1971) and increased resistance of cells and organisms to stress, can be achieved with ginseng, eleutherococcus, and 2-benzyl-benzimidazole (Rusin, 1971), used singly or in combination. Piracetam, an analog of GABA, improves learning, increases resistance to toxins or oxygen

deprivation, and increases bilateral symmetry of function in the cerebral hemispheres. The oldest, most basic therapies, sleep and nutrition, have the same function of restoring energy reserves. Pavlov worked with the simplest stimulants and sedatives, for example caffeine and bromide, to restore normal nervous functions, and of course always considered sensory stimulation essential to maintaining and restoring normal functioning.

The importance of improving protein synthesis is implied by the observation that serum from schizophrenics inhibits protein synthesis in rat cerebral hemispheres, hypothalamus, and cerebellum (Us and Bozhko, 1971).

Several people (e.g., Manukhin and Turnayev, 1971) have suggested an identity of acetylcholine, epinephrine and serotonin "receptors," and this structural-energetic theory similarly would suggest that "specific receptor" psychopharmaceutical approaches lack a proper physiological basis. But studies of psychoactive agents can contribute to a general understanding of cell and brain function, and can possibly support an orthomolecular approach. For example, when excessive cholinergic activity is involved in nervous dysfunction (and excessive acetylcholine can *block* cholinergic synapses, Ilyuchenov, 1971), cholinolytic cell stabilizers (e.g., acetylcholine or tetraethylammonium with the adamantyl radical substituted for the N-methyl group (Kharkevich, 1971) might be used to stabilize nerve function while actual repair processes occur under orthomolecular therapy. The adamantyl radical is also useful in treatment of Parkinsonism and viral infections (Il'iecheva, 1973), again suggesting a general biophysical structuring effect, as in cholinolytic processes.

The Russians have two electronic techniques that may serve as alternatives to ECT (electro-shock) and which may in fact give some insight into the effects of ECT on the

brain. Electrosleep (produced by 5-100 Hz pulses, with peak current of 5-8 mA applied to the eyes--negative pole, and mastoid process--positive pole) has been used in treating "functional disorders of the CNS," autonomic and endocrine functional disorders, etc. (Studnitsyna, 1972.) High frequency (5000-6000 Hz) currents have been found to stimulate the brain (Rubakov, 1973).

In embryonic muscle cells, when the "depolarizing fast acetylcholine receptors" are blocked by snake venom, then the cell's "slow polarizing acetylcholine receptors" are revealed (Patrick, et al., 1972). This type of receptor may be responsible for the trophic influences which maintain high polarization and which seem to be involved in such things as the "Bowditch staircase." Electrical stimulation may act on similar "receptors" in neurons.

Vitamin B_6 is a coenzyme in carboxylation reactions and as such is involved in the synthesis of serotonin from 5-hydroxytryptophan, and also in the formation of GABA (gamma-aminobutyric acid) from glutamic acid. In the "resting" state, cell water seems to be more orderly, as if it had a lower "structural temperature." Some enzymes are inactivated by cold and presumably would be inactive in the resting state. GAD (glutamic acid decarboxylase) has been found to be among these peculiar enzymes, and this is the enzyme which decarboxylates glutamic acid, producing GABA. GABA has been shown to be a mediator of nervous inhibition on the basis of several criteria, including heightened GABA liberation in sleep and near-sleep (Sytinskiy, 1973). This would seem appropriate if the physical state of cell water is participating in brain regulation. During brain "activation" or exhaustion, this enzyme should become more active, producing more GABA and presumably thereby promoting rest and restoration. (Since hydroxylamine is an inhibitor of GABA degradation,

it would be interesting to see what effect it has on psychoses, though it may be too toxic to be practical; the same might apply to hydrazine, which is used with considerable success in inoperable cancer, and often induces sleep as well as preventing cachexia.) The natural anesthetic steroids would probably be the first choice for a chemically induced state of sleep if they could be administered conveniently.

Another enzyme that should be investigated from this point of view is NADase, since it too shows what may be a sensitivity to structure: In cell homogenates, it is sufficiently active to destroy NAD and thus stop glycolysis at the triose phosphate stage (Florey, 1966). It is inhibited by nicotinamide, but is also relatively inactive in the intact brain, at least in nonschizophrenic brain.

Magnetic fields presumably act biologically by acting on the structure of water, and Kholodov has established that a continuous sinusoidal magnetic field has a sedative and inhibiting effect, modifying the EEG and raising the level of GABA in the brain (Speranskiy, 1973). The activity of oxygen increases in magnetically treated water (Speranskiy, 1973), so there might be a direct effect on energy production.

Harmful types of radiation are generally thought to act only by ionization, and many researchers believe that the only harmful effects of such ionization are direct chemical changes in the genetic material. But there are hints in the "Russian paradigm" that small amounts of radiation can have a catalytic or chain-reaction type of effect in materials other than the genes, and that the effects of radiation on cell water might have important consequences for development, enzyme activity, and nerve function. They have demonstrated that microwaves with energy that is "too low" to affect cells according to western paradigms, actually have

clear effects. For example, S. N. Yevseyeva (Voprosy Kurortologii Fizioterapii i Lech. Fiz. Kult., No. 6, pp. 536-540, 1972) reported that decimeter wave treatment normalizes adrenal function and improves breathing in asthma patients. The structure of water appears to be the only aspect of the cell which is sensitive enough to account for the observed effects. Since non-ionizing radiation has these unexpected effects, we should consider whether "ionizing" radiation might also have effects on cell water at unexpectedly small doses.

The Russians have sustained the interest in light therapy that was current in many countries several decades ago, but their research in photobiology is just beginning to get interesting, and hasn't reached the stage of practical therapeutic application yet. Older work had suggested that exposure to red light selectively activates the parasympathetic part of the nervous system, so it is reasonable that Soviet physicians would be especially interested in the types of lasers (helium-neon) which produce pure red light.

V. M. Inyushin has discussed the use of the red laser for therapeutic stimulation of tissues in various diseases involving problems with circulation--"disruption of neurovascular trophic processes"--(Helium-Neon Laser Light in Biology and Medicine, Alma-Ata, 1970. P. R. Chekurov used this type of red light to treat obliterative endarteritis, poly-arteritis, and osteo-arthritis.

The old tradition of Russian medicine, "nervism," which reminded physicians that the brain must always be considered to have a role in sickness and recovery, has been enriched by the work of Pavlov and his successors. The tradition's most valuable lesson for American medicine might be its optimism, based on the idea of plasticity, and especially its recognition that cells (especially nerve cells)

which have stopped functioning might just be in the low-energy state of protective inhibition ("parabiosis"), and able to recover when their energy is restored. Rest, nutrition, and appropriate stimulation are at the center of scientific medicine.

Extracts of glands and other tissues have been used for generations to treat nervous diseases (e.g., Filatov, 1945). Thyroid, with or without gonadal extracts, has been widely used to treat nervous and mental disease. L. V. Polezhaev (*Loss and Restoration of Regenerative Capacity in Tissues and Organs of Animals*, Harvard Univ. Press, 1972) has remarked that some of these treatments for neuropsychic diseases also promote regeneration, growth, and multiplication of nerve cells. Filatov, Polezhaev and others have clearly demonstrated regeneration of nerve tissue in the brain, cerebral cortex, and optic nerve.

I think it was around 1950 that I first read of Polezhaev's work with stimulated regeneration. Ever since then I have not only admired the scientific intelligence of his work, but I have followed with dismay the way most scientistists ignore, suppress, or ridicule his important basic discoveries. Regeneration relates so closely to aging research, it seems to trigger the same anxious and hysterical response. Apparently, in repressing the fear of death, many people develop a displaced fear of the possibility of solving the riddle of aging and death. When work of this nature becomes acceptable to our culture, I predict that its history will be reinvented, and its nature somehow transformed so as to isolate its fearsome origins, and keep them repressed.

Ultimately, therapy for the mind implies therapy for the body and the world.

CHAPTER 13
IDEAS ON ELECTRONS IN CELLS

The downfall of Gurwitsch and his mitogenetic rays seems to have been a result largely of his proposal for overcoming the criticism that such weak rays couldn't penetrate so far through living tissue: What he suggested was strange sounding to people who knew a little physics. He proposed that the radiation was comparable to a chain reaction, in which the products of the first reaction initiate a second, etc., except that all the reactions and their products are the same. An adequate unit of radiation striking a cell may either cause that cell to divide, or enable the cell to release a radiation or both." What otherwise would be a barrier to the radiation may, by resonance, emit a "secondary radiation." The properties of the secondary radiation are essentially those of the primary radiation. "In this way the original stimulus from the external source can be propagated through the interior of the culture or tissue." (Crile's discussion of the rays.) "...it was found that the radiation emanating from the root tip originated in the onion sole. The transmission of these rays lengthwise through the root apparently did not impair their power to stimulate cell division, even beyond the tip of the root." But "the root in cross section was only slightly transparent to the radiation." In the early 1930s the Gurvitsches (A & L) studied the spectrum emitted by nerves and by chemical solutions subjected to mitogenetic rays from an external source:

> Substances which, in undergoing decomposition by fermentation or hydrolysis, emit at that moment a radiation of a definite spectrum, respond to irradiation by an identical spectrum, by emitting the same spectrum, as a secondary radiation.

> In case of irradiation with a different spectrum, the secondary radiation is absent or at any rate very weak.
>
> This fact, unexpected enough by itself, becomes more difficult to interpret if one considers the results of monochromatic irradiation. It is not merely the band in question which reappears in the secondary spectrum, but the latter in its entiretly, in infraction of Stoke's law. If we take, for example, the band 2170-2180 A of the glycolytic spectrum as irradiator for a solution of glucose, the secondary spectrum emitted by the latter contains also the shortest band (1900-1920) belonging to the glycolytic spectrum.
>
> (From L'analyse Mitogenetique Spectrale, Paris, Hermann, 1934.)

O. Glasser and M. Schott conclude that the behavior is :"paradoxical" and the theories are "difficult to accept." Others proposed a diffusible substance that would account for the induction of mitosis, but this conflicted with Gurwitsch's original observation, as well as later experiments; He noticed that the mitoses appearing around a wound in the cornea could be blocked on one side in a way that resembled a "shadow"--the borders were straight, which would not be the case if molecular diffusion were the inducer. This was what led him to postulate mitogenetic radiation. Later, a cellophane membrane was used to separate the source and the receiver, but opponents showed that the film was permeable to gases. So Gurwitsch used a quartz sheet for the separation, since this would allow u.v. radiation to pass, but his opponents continued to insist that even the quartz must be permeable to a chemical inducer.

In a symposium (Naval Research Lab, Washington, D.C., Oct., 1973) A. L. Schawlow (Stanford) predicted that

laser light will be used to control chemical reactions by tuning in on the energy levels of particular molecular bonds. If Gurwitsch had used these terms to describe his phenomenon, it could have been more easily accepted as a kind of catalysis, releasing chemical energy (or biological energy), rather than as a kind of fluorescence which would violate Stoke's law. (Even conventional theorists recognize cases in which thermal energy can contribute slightly to the excitation process of photoluminescence. Schawlow also commented that "anything will lase if you hit it hard enough," and demonstrated with a picture of lasing jello.

Lasing gelatin may be more than a joke. The unique photoelectric properties of protein are recognized in the use of gelatin in photographic emulsions. Szent-Gyorgyi has written a few books arguing that the properties of life depend on the electronic or photoelectric properties of the protein-water gel. Fluorescence and resonance have been proposed as a possible basis for nerve function. The fact that water is ordered in cells, and appears to be arranged longitudinally in nerves would seem appropriate if the gel structure is involved in the longitudinal conductivity of nerves. The observation that the gross conductivity of the brain is decreased by exhaustion (Crile, p. 200) and that the brain's electrical gradient is lower in fatigue led me to consider an electronic approach to consciousness, which relates the "Hopkins-Szent-Gyorgyi-Racker electron pool" to the states of consciousness, as well as to mitosis.

Telkes found that the protein fraction of tissues produced chemiluminescence when oxidized, especially in the presence of an added fluorescent molecule such as fluorescein, eosin, or rhodamin. Commercial gelatin also produced some light. Using filters, u.v. frequencies were demonstrated. Some organs consistently produced higher or lower intensity of light. The significant observation,

though, was that exhaustion of the animal, or adrenalectomy, diminished the chemiluminescence of some tissues.*

For the luminescence to be altered by a procedure such as surgical shock, it seems that the source must be in electrons that are much more labile than those in ordinary chemical bonds of the protein. (The electrons of free radicals are relatively active, but chemiluminescence produced by free radicals would be expected to increase as a result of injury.) Szent-Gyorgyi has proposed some likely sources for the electrons which are able to reduce large amounts of glutathione when only protein seems to be present as a reductant. It might be possible to determine whether these are the same "kind" of electrons in both cases by oxidizing with glutathione first, then using Telkes' procedure and seeing if luminescence is less. Also, the "laseability" of a protein solution might be altered after it has donated its electrons to glutathione: If so, this would increase the reasonableness of Gurwitsch's idea that light-resonance in tissues stimulates cell division, since Szent-Gyorgyi and others have already implicated the electron-pool and sulfhydryls in mitosis.

Crile's observation that exhaustion, conductivity and tissue fluorescence are related suggests that Pavlov's idea of "transmarginal inhibition" resulting from over-stimulation, and being involved in psychosis, could be another aspect of the same cellular event. It is now known that this kind of inhibition involves high levels of ammonia and other metabolites in nerve cells, a low level of energy-rich substances, and changes in proteins resembling denaturation. Niacin's role in schizophrenia (Hoffer and Osmond) might result from its involvement in reducing glutathione, which is in equilibrium with the "loose" electrons of cell proteins.

The existence of long-range order in water has opened up a new way of viewing effects of "low energy" light on chemical reactions: Solvent modifies reactions, solvent has memory, solvent can respond to energies too low for the reacting molecule itself to respond to. The long-range "domains" in the solvent system can act as a sort of antenna, absorbing energy that isn't strong enough to directly act on chemical bonds. Also, the existence of laser technology is forcing people to recognize a little more complexity in physical-chemical processes: Stokes' law and the conservation of energy aren't being threatened if we suggest a laser powered by metabolic electrons.

In "On distant intercellular interactions in a system of two tissue cultures connected by optical contact," V. P. Kaznacheev, et al. (Transactions of the Moscow Soc. of Naturalists XXXIX, p.224, biol. ser., section of biophysics and radiobiology) have reported effects much more specific than Gurwitsch's ("morphological manifestations"), transmitted through quartz. It's time now to give up the absurdity of claiming that inductive molecules are crawling through the quartz window. (The doctrine that molecules and large atoms can go through glass is a *deus ex machina* that is used with disturbing frequency by supposedly rational established "scientists," to dispose of facts that would force them to change their dogmatic beliefs.) If there are cellular changes induced by events on the other side of a window, we should start investigating the mechanisms by which such rays might act. The main reason for not investigating such problems is that our scientific culture is still tied to old ideas of atomism, reducing everything to simplified local interactions.

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*George Crile, The Phenomenon of Life, a Radio-electric Interpretation, W. W. Norton & Co., N. Y., 1936.

CHAPTER 14
THE BRAIN AND MAGNETIC FIELDS

When two subjects such as the brain and magnetism--both still very open to speculation--are combined into a new field of research, we can expect the subject to be both imaginative and controversial. Fundamentally new processes, materials, and interactions can be expected to separate the past-centered from the future-centered scientists, provoking bitter disputes. In such circumstances, it is probably best to begin with an aspect of the subject that has at least some acceptance in the West, and to work from there toward the more general picture held by Soviet investigators of the effects of magnetism on the brain.

It is universally accepted that water has structure, that it is not an "ideal liquid," and that this structure is responsible for some of the peculiar properties of water. But this structure is usually thought to be only on the level of "flickering clusters," lasting about a millionth of a millionth of a second, and involving only a small group of molecules in each cluster. In 1926, Shereshevsky (an American) discovered that water and other liquids in small glass tubes behaved as if their structure had increased, that is, their vapor pressure became much lower than normal so that the liquid would condense in the tube at pressures that should cause it to evaporate. In Russia, Boris V. Deryaguin was demonstrating that even flat glass surfaces alter the behavior of water at a considerable distance from the glass. (It showed structural elasticity at distances under 900 Angstrom units.) After many years of experience in the study of water, Deryaguin discovered another important phenomenon: water could "remember" having been in the

frozen state for as long as a day after being melted (it had different properties between vibrating glass plates).

Several years ago in an industrial process which involved "floating" ore with magnets to refine it, the water which had been magnetically treated was found to be more capable than ordinary water of holding in solution the minerals which are deposited as "scale" inside water tanks and pipes. This led to many investigations of the properties of magnetized water, and to reports that its density, surface tension, and possibly its refractive index are higher than ordinary water's. It is interesting that in the 19th century, the Baron Charles von Reichenbach claimed that magnetically treated water had biologically detectable properties, as did water containing ice. Reichenbach believed that there was a common ("Odic") energy underlying the function of crystals, magnets, electricity, life, etc. Popular culture in the United States has been assimilating some of these ideas recently. The results of Soviet science parallel those ideas in many ways.

There has been speculation lately regarding a possibly new state of water discovered by Deryaguin. The material forms when water condenses at low pressure in capillary tubes. It resembles a dense, syrupy glass, suggesting that its structure is molecular, probably the result of additional substances dissolved from the glass tubes. It shouldn't be confused with "magnetized water." (Deryaguin's group has recently discovered another phenomenon of condensation at low pressures, in which carbon vapor grows into diamond crystals.)

One response to these observations might be "if we don't even understand water very well, we might as well disregard it and study biochemistry as if water were just a solvent, just a convenient medium in which the crucial chemical reactions take place." Another way of responding

is to say "the more complex water is, the more chances we have to find a really adequate description of what an organism is and why water behaves as it does in the living material." The difference is whether we treat strangeness as a threat, or as an opportunity. Unfortunately, many biochemists feel threatened by the assertion that "there is no biochemistry distinct from biophysics," and that particles can't properly be considered in isolation from their environment.

Starting--as many Soviet scientists do--with the recognition that both water and organisms are sensitive to magnetic fields, many questions present themselves. What will treated water do to various organisms and tissues? Which organisms and tissues are most sensitive to magnetism? What does temperature do to the magnetic sensitivity of a tissue? Does an alternating field have a special effect? How did the earth's magnetic field affect evolution? Does the geological record of periodic changes in the earth's magnetic field have something to do with the sudden appearance of new phyla of plants and animals? Can we be aware of changes in magnetic fields? Do animals orient themselves by the magnetic field? Can magnetism be used in medicine? Some of these questions have been partly answered, and others are just now starting to be investigated.

In animals, the most obvious trend in evolution is that of "cephalization," the increasing centralization of nervous processes in the head, and the growing complexity and size of the brain. At the same time this anatomical centralization occurs, there is also a metabolic tendency toward a higher efficiency of energy production. This change of efficiency apparently represents an increase of structure in the cell, and structure in general corresponds to the electrical potential of the cell. It has been known since

the end of the last century that a magnet will delay a nerve's response to an electrical stimulus, as if its structure had been preserved momentarily. If we think of the magnetic field as stabilizing the "head state," it occurs to us that the earth's magnetic field must have been an important factor in evolution, supporting or promoting "cephalization."

Yuri Kholodov has found that higher organisms tend to be more sensitive to magnetism than lower ones, and that he most sensitive tissue is nervous tissue, especially the brain and the glial cells, which are thought to be involved particularly in memory processes, and to provide some kind of metabolic support for the neurons. He found that the glial cells enlarge under the influence of magnetic stimulation. Recently, another magnetobiologist has found that the testes are also exceptionally sensitive to magnetism. Ordinarily, we don't think of testicular tissue as being uniquely "structured" in the sense that nerve and muscle are. However, in higher animals the testicles are carried in a scrotum, which keeps them slightly cooler than the rest of the body. At normal body temperature, the testes are unable to function properly; neither hormonal nor sperm-forming processes are normal at the higher temperature. Besides slowing the rate of chemical reactions slightly, this small amount of cooling would tend to increase the structuring of cell water. So the two peculiar tissues, testis and brain, apparently have unusual structural requirements for functioning normally, and they are the two tissues most sensitive to magnetism.

To emphasize the importance of cell structure in magnetic sensitivity is not to imply that electronic or free radical processes may not be crucial factors in that sensitivity--magnetic fields do cause measurable changes in electronic processes such as oxidation. Rather, what is being suggested is that there is a reciprocal relation between

structure and these electronic processes, and between both of these and the magnetic environment.

Many fish, which aren't normally considered to be "electrical," generate a very weak electromagnetic field around themselves, and are able to use this field to detect even small objects in the water around them. How they sense the changes in the field isn't known. Similarly, sharks can detect incredibly weak fields, such as those created by a minnow buried under sand, even at considerable distances. (It is apparently the electrical field of a wound which attracts them, rather than just the smell of blood.)

In Mexico and Central America, where earthquakes are common, it has been recognized that animals can in some way sense a coming earthquake. It has been suggested that they are detecting alterations in the electrical or magnetic conditions of the earth which precede the shaking. In Mexico, "everyone knows" that thunder and lightning (or colored flashes of light) precede or accompany earthquakes, and similar but earlier disturbances might be what animals sense. For years, Soviet geologists have been studying the ability of dogs to "smell" minerals. Some of them believe that the dogs are actually detecting some electromagnetic property of the material, since they can find ore which is covered by several meters of other minerals. Dogs have been trained to recognize the "smell" of a gold ring, and are then able to pick out samples of ore which contain even small amounts of gold.

The same increase in the efficiency of energy production which Verzhbinskaya (see chapter on the orienting reflex) found to occur in the brain in evolution and in the state of mental alertness, has also been found to occur in many tissues under the influence of a magnetic field. Of course, high efficiency energy production will have survival value in many ways, but if the metabolic gradient is the key

to cephalization, and if the brain is the most sensitive to this kind of stimulation, it is clear that magnetism will be an environmental support (or a "selective pressure") for bigger and better brains.

This observation might also suggest a new approach to the fact that the appearance of new phyla coincides with the appearance of a new geological magnetic polarity (found in rocks from deep borings), after a short period (a few thousand years) in which the polarity disappeared from the geological record. The standard view has been that, since the magnetic field protects the earth from intense radiation, these periods without magnetism allowed mutations to occur as a result of radiation. However, the new phyla that appeared were of a higher complexity than those which preceded them, meaning they contained *more* information, and we know that radiation produces mutations by the destruction of information. (But the idea that the magnetic field protects the earth from radiation is itself questionable.) If magnetism stabilizes the higher functions and structures of the brain, then we have at least the beginnings of a sensible interpretation of the fact that the earth's magnetism has some correspondence to major evolutionary advances.

If we could fill those gaps of thousands of years with a special *magnetic* event, other than the disappearance of the earth's magnetism, we would have a better argument for the importance of magnetism in the development of brains. N. A. Kozyrev has provided a theoretical reason for believing that planets and stars, including the sun, are evolving toward higher energy states, rather than dying down, and of course such evolution would include changes in magnetic field, as well as other changes, such as volcanic action.

Kozyrev proposed time as a real participant in physical processes, contrary to the dominant 19th century

idea that it is only an abstract framework in which events happen. As such, time would be a source of energy or order. He first proposed it in relation to some problems of stellar energy, saying that time could contribute energy to stars. He calculated the amount of energy time could add to a smaller body like the moon, and predicted that there should be some volcanic action on the moon. When he obtained photographic evidence of red eruptions on the dark moon in 1959, he was generally ridiculed--for example, an eminent American astronomer years later was still referring in his lectures to "that Russian's drunken hallucinations." Nevertheless, his observations have been duplicated by many others, and also have been supported by the unexpected discoveries made by instruments placed on the moon. Reviews of astronomical records have subsequently found that there were previous observations of red lunar eruptions, but without photographic proof.

Kozyrev has turned his attention to the larger planets, finding further verification for his theory of evolving planets, internal energy, and magnetic fields. One of his strangest predictions relates planetary spin to the "heart shape" (flattened top, bulging bottom) of planets. On the level of organisms, he suggests that biological form and "time-energy" may interact. This would be a direct mechanism promoting the evolution of higher order, but his theory also fits nicely with the known facts suggesting magnetism as a link between cosmic evolution and the evolution of life forms.

Accepting Kozyrev's general theory, we might be able to interpret the magnetic gaps in the geological record as periods of instability in either the earth's or the sun's magnetic field, and to suppose that the actual field experienced by organisms was very high, though it failed to

be recorded in the rocks because, for example, of the earth's constant movement through the sun's field.

There is a very practical problem that grows out of the interaction of brain and geological and solar magnetism, namely, the fact that solar "magnetic storms," or sunspots, are followed by magnetic disturbances on the earth, which result in high rates of nervous and emotional diseases, accidents, suicides, strokes, and heart attacks. At present, all that can be done on a mass scale in the Soviet Union is to have nationwide medical and safety alerts in the days following sudden bursts of solar activity. Experimentally, however, special isolation chambers are being used to protect patients from these magnetic storms. (It's important to remember that their scientific culture, which is so advanced in many ways, exists in a culture that is still economically backward, making the application of scientific discoveries especially difficult. Besides the slow bureaucratic processes, most physicians don't have the resources to apply modern knowledge.)

Since it is a fundamental principle of Russian medicine that the brain must be considered as a possible factor in all diseases and recovery processes, the magnetic environment is also being considered as a general factor in health. Its action on the brain is very important, but its direct effect on other tissues, such as white blood cells and the liver, etc., is also being studied. It is known that the weak fields of interplanetary space can cause reduced phagocytic activity of white blood cells, but it isn't known yet how much this effect is mediated by the brain.

Although what is now known suggests that a stronger magnetic field might contribute to improved brain function, the present emphasis in the field of "brain improvement" is on techniques that can be immediately implemented on a mass scale with the greatest benefit to the

public, for example to avoid brain deterioration resulting from work conditions.

Western scientists--basing their opinions on studies done in the 1940s in which animals exposed to radio waves showed no gross tissue changes when they were sliced up--said it was foolish to worry about possible harm from the "very low energy" waves of radio, television, and microwave ovens (except when tissue was actually cooked), since there was "no known mechanism" by which they could act on living tissue. The energy was not sufficient to cause a nerve to "fire," they argued, and so it could not possibly act on the brain. Meanwhile, since the Russians tended to think of nerves as complexes of water, macromolecules, and adsorbed small molecules rather than as "bags full of chemicals," they looked for more subtle effect, and found them. For example, they found that microwaves could relieve epilepsy in animals. As usual, the response in the U.S. was that they couldn't have achieved such a result, because it wasn't possible. As a result of such studies workers are protected from all kinds of electromagnetic waves, not just from high energy x-rays and nuclear radiation. Incidentally, a similar policy exists in regard to sound, since equally "impossible" effects of sound on body chemicals and structures have been observed. Long-range ordering of water and solutes is the mechanism which makes these effects possible, but such order doesn't exist as far as most American scientists are concerned. (The reasons given for dismissing evidence of such order are ultimately so flimsy that, to an independent observer, the motivations seem palpably extra-scientific. Because of the dependent nature of the science student, observers are seldom able to be independent.)

Recently, it was found that boiled water in the diet allowed blood cholesterol levels to become much higher

than when structured water--either magnetically treated or from ice--was used exclusively. Coffee itself doesn't raise blood cholesterol, or even necessarily blood pressure, so people with abnormally high cholesterol might find it helpful to use unboiled water. (But elevated cholesterol is almost always just a sign of low thyroid function.)

The best results in brain improvement, at present, have been achieved by conditioning mice to reduced air pressure, equivalent to an elevation of 10,000 feet. Brain function and its metabolic efficiency improved. The mechanism responsible for the improvement might have been both a simple adaptation (multiplication of mitochondria, as occurs in increased thyroid function) and an increased structuring of the protoplasm which might be expected at slightly reduced pressure. High pressure apparently causes a sort of "melting" of the protoplasm, and extremely high pressures inhibit oxidation.

When more has been learned about magnetism, water, and the structure of protoplasm, so that long-range safety is assured, we can probably expect to see the establishment of regular brain improvement resorts, using the combined effects of structured water, mountain air, electrons, and environmental magnetism. It is possible that the optimum conditions already exist in some regions, and account for the unique vigor of the inhabitants.

The brain is so important in the aging process, magnetic stimulation might lengthen life by intensifying brain function, causing sounder sleep, and improving repair processes. Light therapy is probably very important for sustaining and restoring optimum brain function, and I plan to write about current Soviet research in photobiology in the future.

If even pure water is capable of magnetic and structural "memory," then the more complex, stable, and

variable structures composed of water and biological materials would seem to be an ideal basis for the rich storages of consciousness. Soviet nerve biologists are investigating these subtle inner changes of nerve cells. In the new science that is emerging, everything is taking on an integral kind of meaning, and things become easier to understand as they become more complex.

CHAPTER 15
THE "EFFECT OF PERSON"

Someone noticed that when a person enters a room where a dog is hooked up to recording devices, the dog's pulse and respiration become slower and deeper. People respond the same way to the approach of another person. This response is called "Effect of Person." The changes are similar to some of those occurring in sexual excitement.

Slowing of the heart beat is produced by acetylcholine, which is release by the parasympathetic division of the nervous system. Reich and others have described parasympathetic function as being "expansive," in contrast to the "shrinking" function of the sympathetic nerves, as in fear. Both of these functions are meaningfully related to the central nervous system, the cerebral cortex, and to the perception of outside events.

To understand the Effect of Person, and sexual excitement, and love, we need some better perspectives on the meaning of nerve functions and on the nature of their integration with each other and with the experienced world. To get these new perspectives, we will have to work with both our perceptions of ourselves and our "objective" observations.

In the feeling of love, our inner body-space seems to expand, and we seem to be filled with the other. At the same time, we see the world with the perspective of the other, as if the world were enclosed in the other:

> And within it opens into a World
> And a little lovely Moony Night.

Another England there I saw....

Another Maiden like herself,
Translucent, lovely, shining clear,
Threefold each in the other clos'd--
O, what a pleasant trembling fear!

O, what a smile! a threefold Smile
Fill'd me, that like a flame I burn'd;
I bent to Kiss the lovely Maid,
And found a Threefold Kiss return'd.

In this process, the body's pace changes as the feeling of space is altered. The cerebral hemispheres are important for the perception of space, and they also are involved in "setting the reflexes," probably largely by stabilizing individual nerve cells at a certain energy level, raising the "thresholds," for example, by raising the ATP level. Each hemisphere has a trophic influence on the other, involving a similar raising of the energy level. Sleep (via GABA) also tends to raise the energy level. (Chemicals which elevate GABA--hydroxylamine, piracetam, for example--improve learning; piracetam is known to increase bilateral balance of the hemispheres.)

Lowering the energy charge (exhaustion, some psychoses) apparently causes a perception of shrunken space; if we could relate energy charge to the two aspects--shrinking and expanding--of the autonomic nervous system, we would have a simple way to understand their effects. Since high activity of ATPase could lower the energy charge, chemicals altering this enzyme might have these general effects on perception and function. (ATPase seems to increase in the "melted" state.) Adrenaline--the chemical characteristic of sympathetic activity--decreases

the activity of ATPase. This is one way of looking at the connection between the sensation of space and the shift of physiological pace.

Another way of looking at the same interaction of space and pace: Big things always seem to have a more leisurely pace than little things--stars and atoms, elephants and mice. It may be that perception of space and regulation of motor rhythms are part of a single process. Bashkova and Zakharyants described a boy's symptoms following an attack of malaria that illustrate the connection of pace and space:

> Objects began to seem much smaller in size. The patient's perception of speed was no longer correct: Everything seemed to him to be taking place faster (people, for example, did not walk, but ran). For this reason he too began to do everything very quickly. After treatment with quinine, these aberrations disappeared. (Pages 173-174, *Space and Time Perception by the Cosmonaut,* Leonov and Lebedev.)

In the anxious sympathetic state, nerve threshold would be lowered, and reflexes would be triggered more easily: This would increase the pace of activity, but since the energy charge wouldn't return to the highest level, the action would be smaller. This would presumably apply not only to heart-beat and respiration, but to other reflex actions such as orgasm.

The thyroid hormone keeps the cellular energy high, the adrenaline low, and reflexes strong. It undoubtedly has an important effect on both perception and responses.

In the high energy, expansive state, with thresholds raised, a strong stimulus could evoke a strong response. Things are bigger, possibilities are greater.

The events following orgasm--fusion of worlds and sleep in particular--are where "Effect of Person" or the first stage of love becomes transformed.

CHAPTER 16
RESOLUTION AND TRANSFORMATION

In mutually stimulating interaction, the hemispheres of the brain seem to be generating perception of space (and continuity through time) at the same time that they are "setting reflex thresholds," creating the conditions for integrating emotions with the world.

Enlargement of perceived space corresponds to dominance of the parasympathetic part of the vegetative nervous system (among other things).

Both loving and sleeping produce this "expanded," parasympathetic dominance. In loving, in any mutually affirming human interaction, there is an interaction of perspectives on the world. In each brain, the interaction of two hemispheric perspectives helps to generate and amplify our consciousness of the world. In the loving interaction of perspectives, a similar generation and amplification of consciousness can occur.

As we feel that we are being affirmed and loved by another, we feel that the other person is expanding us, and filling us; our body shifts toward parasympathetic dominance, skin gets pink, eye-lids and gaze may drop--Marcel Proust described the feeling:

> ...filling me with a precious essence; or rather this essence was not within me, it *was* me. I had ceased to feel myself mediocre, contingent, mortal....
>
> (*Swann's Way*)

At the same time, we begin to see the world with their perspective. This centering on the other person probably

happens to some degree every time we understand something new presented by another person--the process of forming a dominant, in Ukhtomskii's language. If our brain "forms a dominant for" the other person, that person has really come into us, and we can see the world from their perspective.

Structurally, this process could be practically the same as that of using the two cerebral hemispheres to intensify awareness. We would have two perspectives on the world, and we would try to synthesize them into one world. Difference is potential, and would "rouze our faculties to act," increasing energy level, or tension. Every "message" is a problem, leading us toward resolution.

The sudden turning of perception at orgasm seems to involve a transformation of both people, each achieving a synthesis of the two dominants. In "The Crystal Cabinet" Blake described another less satisfactory kind of outcome:

> I strove to sieze the inmost Form
> With ardor fierce & hands of flame,
> But burst the Crystal Cabinet,
> And like a Weeping Babe became--
>
> A weeping Babe upon the wild,
> And Weeping Woman pale reclin'd,
> And in the outward air again
> I fill'd with woes the passing Wind.

In this case he came out where he had been "caught" in the first place, "upon the wild." He had been "lock'd up," and felt a "pleasant trembling fear." I think he meant this as a caution against a certain kind of love-making, in which you end the same as you began, only worse. What fails to happen is the transformation from one world to another--I

think because of the attitude of trying to "sieze the inmost Form," being locked up, etc.

Every real action causes a certain amount of growth. Being filled by another person can be thought of as "contracting with yourself" for a large amount of growth. If we are afraid to become someone new, instead of making the transformation we have to fall back to the old self and the old world; we fall slack. Crying involves a strong parasympathetic reaction, and is a way of discharging the expectant expansiveness, but is also an expression of the loss, of the shrunken possibility. (Blake's analysis of consciousness involved distinctions that haven't yet been fully developed in the scientific work of the Pavlov tradition. The Crystal Cabinet doesn't explore the solution to the problem, which Blake believed involved the active creative Fourfold consciousness.)

Although the orgasm involves some kind of turning of perception (and sometimes brings an urge to start playing or making something) it usually turns to dreamy sleepiness. A pattern of cortical excitation tends to become inhibited, according to Pavlov. In sleep, tension is low and parasympathetic dominance is strong. The pattern of the dominants, and of the resolution would remain in the cortex, probably relating to dream activity, possibly with an inverted or "halo" relation to the original form of the perspective-dominant. The resolution and transformation would continue to develop during sleep.

Healthy children always wake up with an eagerness to get back to the world--the world seems new and fresh.* Salvador Dali has studied sleep and dreams more than most people, and has some useful insights:

> Men have attempted to interpret dreams, and even to guide them, but never yet have men

> attempted to use sleep to guide and to control artistic creation which is to be executed in a waking state.
>
> ...you guide yourself hypnotically toward the concentrated objective of synthesis....
>
> Every enforced inactivity, before the impatience to act, becomes accumulated into creative force which, so to speak, is purified, directed. The essences separate into their hierarchies, and sleep, oriented in the direction of the realization of desire, ferments, sparkles, miraculously resolves itself and selects. What you prevent yourself from doing and force yourself not to do, the dream will do with all the lucidity of desire and without any of the blindnesses consubstantial with your champing gluttony.... But in order to enable your dream to work in peace you must cretinize yourself by the "hypnotic doubt" of your sensations, and the infantile game of discrediting the evidence of your senses by means of the three sea-perch eyes suffices, even for the most adult spirits, to encourage it to seek the most natural paths to an effective oniric solution.
>
> (*50 Secrets of Magic Craftsmanship.*)

What Dali has perfected as a practical technique for achieving a new synthesis is probably a basic natural function of the sleeping brain: To transform multiple perspectives into a single new perspective. Dali says that Plato described the last sleep of dawn as "the sleep of truth." Good sleep does promote true perception.

I think this is an important part of what happens to the person following orgasm: The old self, the old world are transformed by interaction with the loved person. The assimilation is probably completed and stabilized by sleep.

Sleep and an active learning state are both fostered by elevated levels of GABA, the nerve-quieting substance, and the functionally related hormones, progesterone and thyroid.

The depth of transformation hasn't been investigated, but it seems likely that it includes even the cellular trophic influences.

*At puberty the slack can accumulate--children advanced by regular increments, but after puberty culture inhibits change and growth, while the Effect of Person becomes huge. Sleep problems, rigidity & apathy could result.

CHAPTER 17
DREAM ENERGY

Where do you draw the line between living and dead, between conscious and unconscious? Much of Western Christian thought has been concerned with this question--"was Jesus a man or a god?" "What distinguishes man from the animals?" etc. The tendency has been to draw the dividing line higher and higher: First, the human soul separates us from the beasts; then, our reason; next, language, use of tools, etc.; next, grammatical use of language; finally, some people are even refining the sense of "grammatical use of language," so that chimpanzees won't share our humanness when they create original sentences.

Another, "underground," line of thinking has existed in the West: Paracelsus, Behmen, Blake and G. W. Crile. These people have seen sympathies among the substances, a common life in the diversities of nature. Feeling themselves to be fully alive, they see all the material world as being alive in its own way, and knowable because of its inner similarity to human life.

Those who have asserted that nature is only mathematical, that the material world is empty and dead, eventually come to the "Behaviorist" conclusion that people, who are just part of the natural material world, are also empty and dead. They (e.g., Monod or Stent) assert that our historical, cultural and mental (or rather, "mental") life must become empty and dead. A similar doctrine was promoted by kings and priests in the 18th century, to suppress the aspirations of the people.

In 19th century Russia, materialist thinking had a tendency--probably from the influence of Aristotle--to see

matter as being full of possibility, to be intrinsically creative. The plant physiologist, Kliment Timiryazev, could ask the question:

> Does a plant possess consciousness? Let us answer this question by posing another: Do all animals possess it? If we accept that all animals have it, why should we deny it to plants? And if we deny it to the simplest animal, where, at what rung of the organic ladder, does this threshold of consciousness lie? Where is the line drawn beyond which object becomes subject?

Out of this materialist philosophy of life and matter came the great Russian discoveries of the 20th c.: Oparin's coacervate theory of the origin of life; Deryagin's work on long-range structures of water; the "sorption theory" of Vvedensky, Nasonov, Troshin and others, in which cell structure and physiology are unified; and the Pavlovians' work in the nature of consciousness and the brain.

These two philosophies are ultimately a metaphysics of fullness and a metaphysics of emptiness, respectively. (Or we can call them assumptions about the nature of particular things, to emphasize their potential, or not.) We can think of these different attitudes as differences in brain function. We normally have, throughout the day and the night, regular cycles of alternating dreaminess and "motor" activity. These cycles usually last about 90 minutes each. We can think of the active part of the cycle as being a focus of excitation, as described by Pavlov, which is surrounded and defined by areas of inhibition. Discrimination is achieved by this process of selective suppression. The focus of excitation and discrimination exists in the brain as an

actual center, analogous to the "centers" or "analyzers" for various abilities, which become more sharply refined in evolution.

With prolonged discriminative learning, Pavlov noticed that the point of excitation becomes fatigued, and shifts to inhibition--this can lead to a hypnotic state, or to normal sleep. This center of inhibition then, according to a law described by Pavlov, becomes surrounded by excitation in a reversal of the previous pattern. Since the discriminative inhibition was structured by the learning experience, the excitation which replaces it must have a similar structure. This seems to explain the indirect way in which dreams relate to the preceding experiences. What was purposefully ignored is now attended to; awareness becomes expansive, and works over the background material, unifying it, strengthening the focus which was established in the preceding phase. Distant and seemingly trivial aspects of the background can now be re-evaluated, and put into a new structure, which may reveal the importance of certain images. Each image, of course, is itself a center of excitation, a "dominant," and as such exists in our memory as an organizing influence. Working from a certain strong center--the core of the dream--we approach and test other image centers for their relevance. Thus, the insight with which we began to dream may be small compared to the discovery that is established during dreaming. This is a kind of recruitment--of image, of dominant, of excitation, of information.

The incorporation of another person, the formation of a dominant for that person, forms a very strong center for this kind of recruitment. When resolution between self and other is achieved, as in sexual orgasm, the delivery of information can be great. We have another kind of gesture, the other person's dominant, with which to scan our own

background of experience--so that the achievement of understanding of "what the other person is" is a real expansion of our own world of possibilities, throwing the light of dream energy into the little-used corners of our life experience.

We can think of the active focus as the peak of a mountain, resting on the background of a dark landscape. A symbol, such as a word, can represent a complex image or concept by becoming attached to this peak. If we do our philosophizing only in this active mode, it is possible to just skims over these mountain peaks, ignoring the dark landscape below, taking the symbols and thinking we have everything. Of course, the geography of the peaks is dependent on the whole. But this mode of thought, seeing symbols as the only reality, can lead to the metaphysics of empty matter, mathematical nature.

If we do our thinking in the other mode, in which the active focus becomes inhibited, and exists as the dark pit of a valley, then what we see is the unifying landscape, and we have suppressed the verbal and symbolic flags that were associated with the peaks. Thought then becomes expansive, and synthesizes rather than analyzing. This dreamy mode of thought always tends toward discovery and newness, while the symbolic mode is limited to deduction and sameness.

These differences of thought are differences in brain function: Some people are literally trapped in the verbal-symbolic mode, and their science must conform to their life. If their inner world is only words and emptiness, then it is reasonable that nature for them should be empty and dead. Western science (in its dominant Cartesian form) has based itself on this hollow metaphysics. Fortunately, the Russian tradition, a kind of spontaneous materialism, has produced a different and livelier kind of science. But if

Western scientists find the Russian conception of matter threatening, what must they think of the Russian physiology which criticizes their entire worldview as a brain dysfunction?

CHAPTER 18
THE FLOW OF ENERGY INTO THE WORLD

We can think of psychopathology in terms of energy being given to the perceived structure of self in the world. Generality and intensity are eupsychic, verbalism and vagueness are at the pathological extreme.

How is it that effectiveness and control lead to an alert, energetic, efficient state, and a sense of having no control leads to depression, a neuro-inhibitory state?

When we assert that consciousness is a hologram of body/world we mean that our meanings are like windows, and that the whole is present in, represented in, any part. When we suggest that the hologram has a finer texture than Pribram's model, based on synaptic interference, could give, and suggest that the gel structure of the brain tissue is the location of the hologram, we are suggesting that all of our meanings are present in systems that relate directly to metabolism.

If we think of consciousness as a flow of electrons scanning through a structured, conductive gel, we can see that the flow could be both focussed and energized by events in the gel.

When we see a flow of visual dots on the retina (when we look at a repeating pattern, or flashing light, or visualize depth) we are likely to say "there must be an invisible scanning mechanism, activating cells in an appropriate way," because we use the language of cellular mechanisms for mental processes. What I am suggesting is that the "mechanism" is directly visible as the flow of

consciousness, and that the "tissue" component of the mechanism is experienced as resistance or framework. One of the retinal processes looks a lot like the pattern made by water streaming over the surface of a slightly dirty plate: The flow tends toward symmetry despite the random placing of the points of interference, or in other words the structure is largely a matter of energy processes.

If generalization is insight into the relationships among many particular experiences, this kind of insight will be facilitated by the kind of energetic imagination that allows many experiences to be held in relationship and compared. We can think of a generalization as a kind of "tube" through which we perceive related experiences, and through which we project ourselves when acting intelligently, or making a discovery: This new thing, previously not done, is possible because it relates meaningfully to other events.

Generality is like a lever: An intelligent action is one that has the desired consequences, and we hope a little action will go a long way. Failure to understand when acting means that the consequences won't occur where we expect them to, so it's as if all the lever is on our side of the fulcrum, reaching nowhere, doing nothing. The lever image can be changed to a telescope, looking through it both ways: When we have great insight and effect, we and world seem to be expanded; when we achieve no effect, we feel diminished.*

Our "tubes" of generality are some kind of connection we make among things in our mental space and

*I suspect that this corresponds to the degree of tissue conductivity, energy charge, tissue structure.

time, in our consciousness "field," the flow through structured gels. If we project ourselves effectively and intelligently into the world, it is because our consciousness is able to structure itself sensitively into the world. To be simple--both inside and out--our structures must be extensive, pervasive.

A certain amount of traffic, on many devious roads, becomes a torrent when a direct freeway is built--the surge of mental energy when insight into a generality is achieved seems to result from the same kind of process. In the same way, much less energy will be needed for ordinary functioning when the structure is simple. It's like a long lever, magnifying our action, saving energy.

Internally, the highly structured micro-world is doing the same thing. In alertness, animals use oxygen more efficiently to produce energy (Palladin, 1964), which facilitates uptake of potassium, indicating an increase of order in the micro-structure. Conductivity is higher between front and back of the head when a person is alert or dreaming. Brain amines seem to support these ordered states--clarity of waking experience, as well as soundness of sleep, require sufficient amines. In rats that are made hypoxic, activity of monoamine oxidase decreases and respiratory effectiveness apparently increases adaptively (Khvatova, Rubanova, and Zhilina, Voprosy Meditsinskoy Khimii 19(1), 3-5, 1973. Administration of monoamine oxidase inhibitors improves resistance of mice to hypoxia (Piskarev, et al., Farmakologiy i Toksikologiya 36(1), 48-54, 1973). Adaptation to high elevation not only increases the number of mitochondria (giving a better oxidative capacity), but it can also produce improvement in bronchitis, bronchial asthma, Basedow's disease (obviously oxygen related), schizophrenia, and manic-depressive

psychosis (Mirrakhimov, Klinicheskaya Meditsina 50(12), 104-109, 1972).

Contrast--not only the temporal contrast of sleep-waking--is very important for the quality of our experience. In the "fizzly" dream state of exhaustion/depression, black can't be experienced, because of diffuse background activity. The same amount of energy or activity could produce more intense and pleasant experience if it could be properly distributed according to meaning patterns. An interesting analytic point is that this fizzly state *is* a meaning; the world is flattened and garbled, and we are disturbingly committed to that kind of world, even though we may know it isn't right--it feels terrible, but the meaning is right there. In this sense, the "normal" person is committed to this world, because its meaning is intrinsic, and he probably has never experienced a more intense consciousness. I want to emphasize that the experience is always meaning, and that we ***mean*** garbled if that's what we experience, in the sense that Merleau-Ponty said that we "are doomed to meaning."

The hologram idea implies that the fine structure is meaningfully ordered with regard to the represented world: This is its window-like quality. Its degree of order will correspond to the order which it images, and this order will increase with generality, and decrease with compartmentalization or so-called concretization (actually, what is most general is most concrete). Energy flow and intensity will change as the nature of the field changes. Both energy production and energy flow become more efficient with insight/control. Convoluted flow, like lobotomy, cuts off the perspective, verbalizes and concretizes, but stays open to energy, in a fizzly, soggy way.

Both metabolic and social events (and development, which is both social and metabolic) can influence the wholeness and intensity with which we interact with the world, and can promote an energy-wasting state, or a condition of growth towards greater wholeness and intensity.

CHAPTER 19
ABOUT OBJECTIVE CONSCIOUSNESS (NO DUALITY)

We have a body gradient which becomes more intense with alert consciousness and with higher evolutionary levels. The body has its completion in the environment that it chooses or creates to live in.

A high consciousness, supported by, and probably constituting, a high body gradient, relates more flexibly to its environment, and so has a different environment, a "faster" one. That is, a flexible instrument has a higher "resolving" power for time. This is clearly the case for complex sound perception, particularly language (e.g., see Pribram, *Plan* etc.). In my experience, it's also true for visual patterns that exist only as a development through time--the pattern is visible only when a certain span of time can be held as "present." Twinkling lights, and the little splashes of raindrops hitting the ground are situations where meaningful (wind) patterns can be seen in what "momentarily" seem to be random events.

An inner stiffness slows down the way consciousness resonates with the world, and so results in a kind of skimming of slow patterns from the world.

When we think of "resolving" or discriminating as an actual material resonance process, in which living material resonates in forms corresponding to forms in the world, we have a concept in which the body-mind problem disappears.

Phenomenologists, like Merleau-Ponty, have wrestled with the dualistic interpretive system of our culture, and have made real progress in moving those old categories toward a new, synthetic or unifying

understanding, but as long as the old cultural forms persist, the problem is going to reappear. Even in Merleau-Ponty's later work (*Visible & Invisible*) the holding together he achieved in his more biological writings is only weakly present in an idea like "chiasm."

In science, the concept of resonance has existed for a long time, though it apparently has never been well generalized. Energy, structure, and interaction are essential parts of its definition.

Sonic and electronic resonance are increasingly recognized as being biologically important. The Gestalt idea of spatial representation of images within the brain is gaining strength with the realization that the brain is hologram-like. The vibratory theory of smell and the "fluorescence" theory of vision reveal another aspect f the idea of consciousness as resonance. The hologram model helps us to visualize a many-leveled energy interaction of organism and environment, a resonance. The mind-body problem is thus a scientific problem, and the paradigm is already available in the physical concept of resonance.

The scientists who refuse to touch the problem are bowing to the old cultural interpretive system. Western philosophy has been duped for centuries by the foolish question of subjective illusion and delusion. The "public knowledge" reaction to this idealistic trick (to say that private knowledge is impossible) has thrown out superior perceptions along with the delusions. The common knowledge of what is delusive, the existence of an ordinary language category, "illusion," shows how unnecessary it has been for philosophers to struggle with the idea. History is full of cases of superb perception (e.g., Helmholtz's description of controllable left or right eye function) which were ruled out because they weren't common in some sense. The ridiculous extreme of this sort of thing is the aging

neurology professor who says that the upper limit of human hearing is 14,000 cycles per second, because he tested it himself.

When we can accept consciousness as a material and objective thing, then we can see new meaning in Mach's "there is no illusion." Certain illusions are diagnostic: "The world is always dark," for example, diagnoses blindness.

More importantly, we will have achieved a basis for a better science, in which high generality and high flexibility perceptions are no longer rejected as "merely subjective." They may be diagnostic of a sick paranoia, or they may be diagnostic of a superior perceptual functioning which is strictly empirical.

Recognizing material, objective consciousness forces us to realize that generality is full and experiential, and that generality exists objectively, to be discovered. It empties of meaning the philosophies of abstraction, the idea that "nature is mathematical," and all of the traditional cultural dualities--even the matter-energy distinction is demystified.

CHAPTER 20
END OF SCIENCE?

> And the chief characteristic of the opposite of affirmation-consciousness--I suppose one might call it depression-consciousness--is that when you are in it, it seems *totally convincing;* like a very brilliant liar, it can account for everything in its own terms. Colin Wilson

The scientists of empire are announcing the end of science and art, and of all cultural progress. Their argument is simple: The knowable world is finite, and our knowledge of it grows at an increasing rate. The end must come soon. Some of them say that physics and chemistry are already finished, and that biology will be completed when a few puzzles are solved in genetics--and the general form of these solutions is already known.

For German idealists--like Hegel or Hitler--"our world, our own time" tends to be seen as "the last stage in History." The Golden Age, or the 1000 year Reich, is always just now arriving. At the end of the last century, many physicists were certain that their science was complete, except for a few details.

Idealists see "pure knowledge" as the source of technology, and so technology must come to an end too, a little later than science.

Materialists are more likely to see our time as being near the beginning, not the end. For example, Marx (who borrowed so much from Hegel) said that "real history" couldn't begin until capitalism has been overcome.

I think this observation is more tautology than perception. The term "materialism" describes the attitude that likes to begin with "the matter at hand," "idealism" describes an approach that emphasizes the importance of established ideas. One's place in the world obviously influences judgments as to where truth and value can be found.

Ever since Heraclitus, materialists have emphasized change, while idealists emphasize stasis. "Pure knowledge" is a source of technology, but technology is also a basis for the development of new formalized knowledge. The steam engine was already in common use when Carnot and Joule formulated its basic theory.

What the idealists are saying is that *their* science is nearly complete, and there is no other science. What they imply is that there can never be technologies which conflict with *their* laws. In the Golden Age, science must achieve certainly, otherwise it wouldn't be perfect. Hegel's version of this was: "...the laws of *real* Freedom--demand the subjugation of mere contingent Will."

German idealism has been influential in western science for most of the 20th century, but now scientists in capitalist countries are letting it guide them into cultural fascism.

Geneticists have been the worst offenders. Genetics is popular among bourgeois racists and elitists, and many geneticists have eagerly formulated genetic theories of intelligence on the flimsiest evidence. But seemingly decent "liberal" geneticists are pushing the idealist doctrine about the end of science. The reason for this must be that genetics has so little real subject matter that theoretical formalisms can generate the desired conclusions with little interference from the material world. There is a collection of papers by the great founders of genetics, which is about all that

contemporary geneticists know about the history of genetics. Looking at the data published there, and interpreting it with different assumptions, one can see the breath-taking mystical guidance those men must have had--it wasn't even necessary for them to try to dispose of alternate interpretations, their faith was so great or their vision so narrow. (Nuclear physicists and mathematicians sometimes become geneticists without bothering to study organisms. The engineering approach of molecular biologists can get results of a sort, but the worrisome thing is that some of them don't appreciate the differences between bacteria and people. If a mechanic tried to sell a farmer a "new carburetor for his horse," the farmer wouldn't buy it, but we often buy similarly irrational "solutions" to our problems.)

That narrow vision serves the geneticists as well in political matters as in academic work. They can reach very definite conclusions about the future of science and society without having to study other theories of history and human nature than the one they can derive from their philosophy of science.

In one of these books in which scientists reveal the implications of their philosophy *(The Coming of the Golden Age),* Gunther Stent said "My general argument will follow more or less Hegelian (or, for all I know, Marxist) lines." He proudly admits that he has no understanding of Marxism at all. The real importance of his argument is that it is a central core, the armature, of the dominant segment of Western European and American science.

Stent believes that the "will to power" is what creates progress, by being sublimated into creativity. "...natural selection favored those proto-human genes which produce a brain in which the will to power concept is innately latent." He continues:

> This argument bears some considerable affinity to Noam Chomsky's theory of the origin of linguistic capacity. For, Chomsky proposes that the structure of the human brain embodies within it a "universal" grammar on the basis of which the "particular" grammars of all natural languages have been generated.... From this point of view, the acquisition of language is the product of an interaction between received particular ideas and an innate general logical system.
>
> Here we have touched on a special feature of human evolution.
>
> In having fostered the cultivation of such attributes as curiosity, ambition and imagination, the will to power provided man with the psychological wherewithal to gain ascendancy over his fellow creatures.

The conclusion of Stent's book is reminiscent of (Harvard psychology professor) Herrnstein's argument that class distinctions based on genetic differences of intelligence are going to be intensified with time. He discusses the outcome of the will to power:

> ...the distribution of its intensity among individuals will have been drastically altered. At one end of this distribution will be a minority of the people whose work will keep intact the technology that sustains the

> multitude at a high standard of living. In the middle of the distribution will be found a type, largely unemployed...whose prototype is the beatnik.
>
> At the other end of the spectrum will be a type largely unemployable.... His prototype is the hippie.

Stent compares these classes with Huxley's Alpha, Beta, and Gamma classes in *Brave New World*, which of course were maintained by special genetic techniques.

Not all American scientists are so ignorant and presumptuous: I remember hearing a physiologist express dismay when he heard the "science is finished" line. Physiology is less formalistic science than genetics--could this be because the idealists haven't worked in it? Many geneticists are thinking of applying their talents to brain physiology when they have brought genetics to a close. Stent assumes there are no important physiological problems left outside the brain.

Stent's present profound understanding of the brain includes ideas like these:

> a genetically determined wiring diagram;
> mental limits expressed as the number of nerve cells;
> the brain was not selected for handling deeper problems such as the nature of matter or of cosmos;
> epistemological aspects place consciousness beyond the realm of scientific research;
> it can never be explained.

With the U.S. government cutting science funds, the idealistic nonsense of these influential scientists is especially destructive. Because their line coincides with that of the ruling group, they can probably count on good funding when they move into other fields.

When that happens, what will happen to more materialistic or objective lines of research, such as those that have found that early experience shapes brain development, or that freedom literally makes the brain grow?

I think they will suffer the same distortion and suppression that some inheritance experiments have received from the idealistic and arbitrary geneticists. The inheritance of "acquired" alterations in brain size, such as produced by Zamenhof (transgenerational effects of diet) must appear unnatural and perverse to the idealists.

At a lecture, Professor Stent cited and praised as the basis for his projected work on brain function, two little-known papers in a German publication. These papers were created for the Nazi party as the explicit genetic rationale for killing inferior varieties of people. Stent didn't attempt to distance himself from their political implications.

If a new, freedom-tolerant culture ever comes into being, we can expect a new science and technology to appear, and even new brains allowed to develop in freedom, adequate to "deeper problems" like the nature of matter and of cosmos.

The Soviet theoretical physicist, Kirill Stanyukovich, has used formal information theory to argue against the idea of a "heat death" of the universe, and related anti-materialistic, pessimistic and skeptical ideas. He sees the possibility, the necessity, of endless "upward" evolution of the universe:

> It is impossible for all processes to be reversible. In the long run changes in quantity must lead to changes in kind and a transition to a new state.
>
> Man is still very young. His recorded history spans less than ten thousand years from the most ancient civilizations. Less than fifty years have passed since there emerged on earth a social system throwing open boundless opportunities for man's creative powers, once shackled with social chains.

This optimistic view is an official part of Marxist doctrine, but I think much of it derives from a cultural optimism that has been recurrent in Russian history. Marxism without the rich Russian culture can be a relatively sterile branch of Hegelian philosophy, or a relatively abstract economic theory. Marxism on a foundation of Aristotelian attitudes is less abstract than a marxism that is grafted onto Cartesian and Hegelian ideas. Optimistically, I think this minor aspect of western culture, the belief in an intellectually richer future, can be recovered and expanded into a humane and scientific culture.

CHAPTER 21
MORE GENEROUS PERCEPTION

> Only he who is able to restore the interior magnitudes awakens a resolute will to liberty.
>
> Robert Creegan

> It indeed appear'd to Reason as if Desire was cast out; but the Devil's account is, that the Messiah fell, & formed a heaven of what he stole from the Abyss.
>
> William Blake

I have tried to show how another culture's knowledge can give us insight into our own, and it happens that science and personality are two of the areas in which our culture needs some new understanding. Our mass media, including the schools, have discouraged the critical attitude of wondering why a particular person says a certain thing, and they have actively suppressed the idea that our science and psychology could be tainted by hidden political or financial motives. When a member of the President's Science Advisory Committee expresses an opinion on new sources of energy (e.g., "wind power is for the birds"), we could better evaluate that opinion if we knew he worked as a consultant for General Atomic and Avco. Other "scientific opinions" should also be treated with suspicion, but sometimes the hidden motives will be extremely hard to discover. "Culture" might be defined as a system of hidden motives, and in this case the only way to criticize it will be by getting outside it. Each culture will have special blindnesses and also some areas with great amplitude and richness of vision. Our job, in our own culture, is to open

whatever is closed, to generate possibilities by working on what has been neglected.

Two of our Anglo-American culture-problems--the subject-object dualism and the meaning of time--are given new dimensions by seeing how differently the Russians think about consciousness. If we can learn to be curious about disturbing facts--such as a visual after-image of motion--we can let these simple but peculiar events guide us into new patterns of meaning, new ways of being. For example, by continuing to pay attention to a motion after-image, we are not only learning to see a brain process in itself, but we are forcing ourselves to think of the brain as an energy storage system. Our culture has given us nothing useful to do with the perception, so we learn to ignore it. A culture which centers on time and motion, and which describes consciousness as a reflection of the world will more likely find something to do with that sort of perception.

Understanding ourselves in the light of Pavlov's tradition can be liberating and simplifying, while revealing an unsuspected richness and complexity in psychology and biology. Just seeing that there are observable brain processes that are similar in everything we do--sex, education, research, work, conversation--gives us a sense of orientation towards other beings that could hardly be achieved otherwise.

The Soviet cultures can give us some new questions, and we need new questions in psychology and in other sciences. But beyond learning what they know, we have the more general job of trying to make our culture more humane, trying to discover all the systems of hidden motives. Robert Creegan, referring to such hidden motives in our culture, said:

> Either we shall have more generous order, wisdom-imbued and boldly marshaling all the sciences for healing and for constructing, or we shall have planned disorder, cunningly rationalized, and marshaling deteriorating science, to break personalities and to enslave, or to obliterate, thoughtful peoples.

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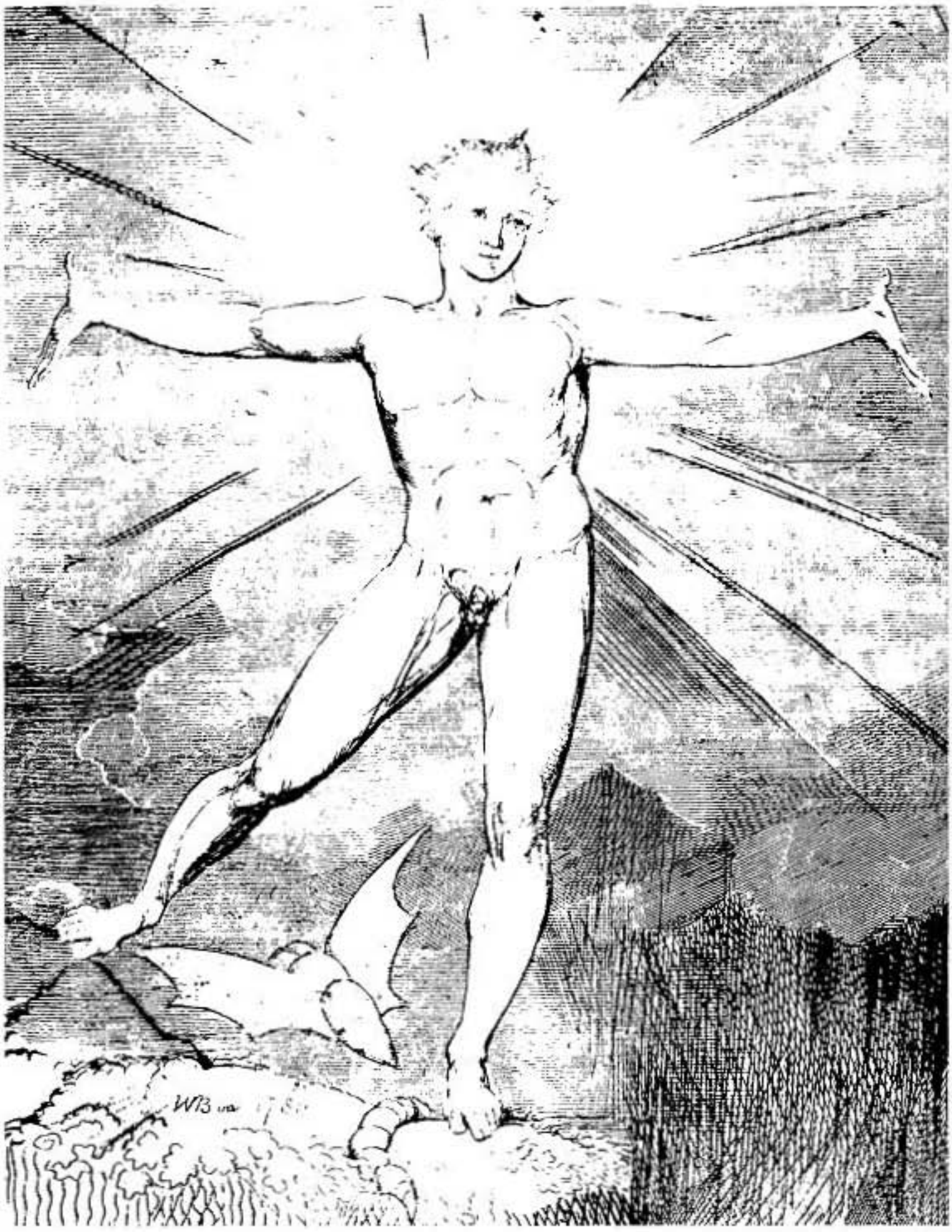

GENERATIVE ENERGY

RESTORING THE WHOLENESS OF LIFE

SECOND EDITION

Raymond Peat, PhD

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INTRODUCTION

In this book I offer some practical methods for solving health problems by increasing biological energy. The methods can be applied by people to themselves, or by physicians to their patients. But energy and individuality and thought are so closely associated that full access to the value of these techniques might require the integrated and balanced approach that can be provided by a new theoretical orientation. I offer some suggestions on the way our inner world can mesh with the outer world, in such an energy-based orientation. And the theory might not be of general interest unless its meaning can be concretized in some specific situations. Other people are working on the same kinds of theories, and other people have worked out parts of the various techniques, but my effort here is to offer something like a "technology of life," which unites theory and practice.

I intend to show that the human substance isn't simply a metastable, transient event, but that it is rather a pioneering probe into a new system. Self-organizing systems decay only if they have assimilated inertia, and--with a little support of the right kind--the centers of degeneration can become centers of regeneration.

Biogenic stimulators, adaptogens, spontaneous healing, cancer, aging, and reproduction are considered here in the light of the best available knowledge of developmental systems in biology and non-equilibrium processes. Besides

having the practical value of bringing coherence into our understanding of some things that have been merely "therapeutic approaches," I hope it will also help to shift the theoretical focus in the study of self-ordering processes away from the informational-statistical, and toward the energetic; to interpret structure, phase and state in terms of energy and history, before considering their abstract, informational properties.

PART ONE:

ASPECTS OF WHOLENESS

"Reason, or the ratio of all we have already known, is not the same that it shall be when we know more. The bounded is loathed by its possessor. The same dull round, even of a universe, would soon become a mill with complicated wheels. If the many become the same as the few when possess'd, More! More! is the cry of a mistaken soul; less than All cannot satisfy Man."

W. Blake

Once we begin to believe in the future, we understand the possibility of learning more, and of being more. We appreciate the unexpected, and we even anticipate the opportunity to confront it.

There is an inertia that makes it easy to over-value present knowledge. If we have enough energy (and enough time), we overcome the inertia. The desire for wholeness can lead us toward a more appropriate kind of science, and also toward a more perfect world.

CHAPTER 1

ASPECTS OF WHOLENESS

Holism is the observation that, although natural objects can be resolved into their parts, the parts are to some extent shaped by their participation in the whole object. For example, in organic chemistry it is recognized that the reactivity of an atom or radical is modified by adjoining parts of the molecule, by the solvent, etc. Holism would never have been named, except that it is so common in our scientific tradition for someone to say "We know all there is to know about the parts (atoms, surfaces, fields, genes, etc.), so we can foresee the result of their combination." Good engineering involves knowing the properties of the materials so thoroughly that accurate predictions can be made about their behavior in new structures, but good science requires a willingness to accept the unpredicted when it occurs. Holism, or a non-dogmatic attitude toward the world, recognizes individual uniqueness, rather than averages, and is likely to look for complex causes (especially environmental influences), rather than too easily ascribing traits "to the genes."

Historically, a reluctance to distinguish our present knowledge from possible knowledge, and to distinguish our definition of something from its real existence and fullest potential, has characterized most of the people who oppose holism, and call themselves reductionists. Consciousness, perception, sensation, pleasure, and intention have often been omitted from the world described by reductionists. If we are going to

understand life and its possibilities, then it seems that we should begin with an appreciation of its "liveliest" aspects, as an essential dimension of our thinking, even if we are going to work with some of its relatively inert aspects, such as viral genetics.

The relation of energy to structure is, I think, the central question of biology. (The importance of the same question for the physical sciences might indicate in a rough way how Haldane's predicted "swallowing up" might occur.) The ideas of resonance and hysteresis, which are only vaguely defined in physics, have to do with the interaction of energy and structure on various levels of complexity and organization, and are examples of physical concepts that can gain meaning and clarity from biology.(1) When energy flows through matter, order accumulates (as a result of resonance and hysteresis, for example), but we hear so much about "entropy," "randomness," and "symmetry" that we forget most of the formative processes in the material world.

Human (and ecological) health obviously should have the benefits of holistic science, but the actual situation is that biology and medicine have become very product-oriented, and holistic considerations are increasingly left to a variety of "fringe" occupations. Many of these alternative approaches are concerned with the idea of "energy" as the key to health, but in general they lack simple and effective methods for optimizing biological energy, and often use counter-productive methods, such as prescribing linseed oil nutritional supplements. In the following pages I will show how some of the most important achievements of ordinary science can be retrieved from the distortions of the medical promoters, and made available for holistic use, that is, for appropriate use.

NON-GENETIC BIOLOGY

The word, "gene," itself contains an ideology, since it implies origin, or genesis, though its main meaning is something like "a unit of continuity." Building on the word's connotation, dogmatic geneticists explicitly stated their "central dogma": that information flows only from DNA to RNA, and only from RNA to protein. When Temin and Baltimore described the "reverse transcription" of DNA from RNA, all of the professional biologists I talked to said flatly that they didn't believe it was possible. Even when no one was threatening the addition of "information" to the chromosomes, the dominant belief among biologists was that development was closely controlled "by the genes," because the body owes its genesis to the genes. Intelligence, body proportions, and senescence were said to be "specified" or "governed" or "programmed" by the genes. The "congenital" condition was often taken as the "genetic" condition. Textbooks said that the maternal influence was only "genetic," because the fetus was "insulated" from events in the mother's body (just as the "germ line" was isolated from events in the rest of the body). Although many kinds of experiment showed both prenatal and transgenerational (see Figure 1) influences of the environment

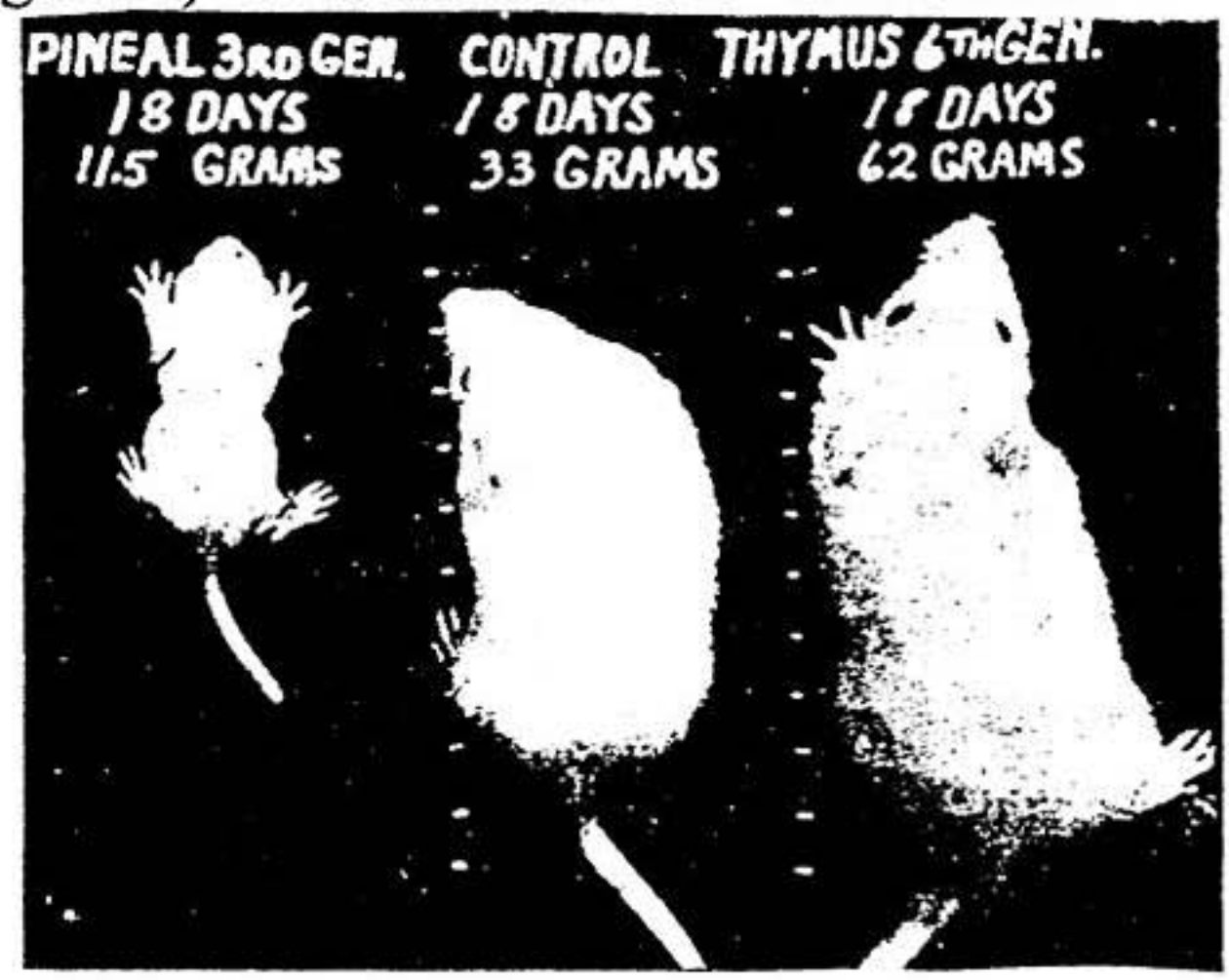


Figure 1. The cumulative effects of feeding glandular tissue.

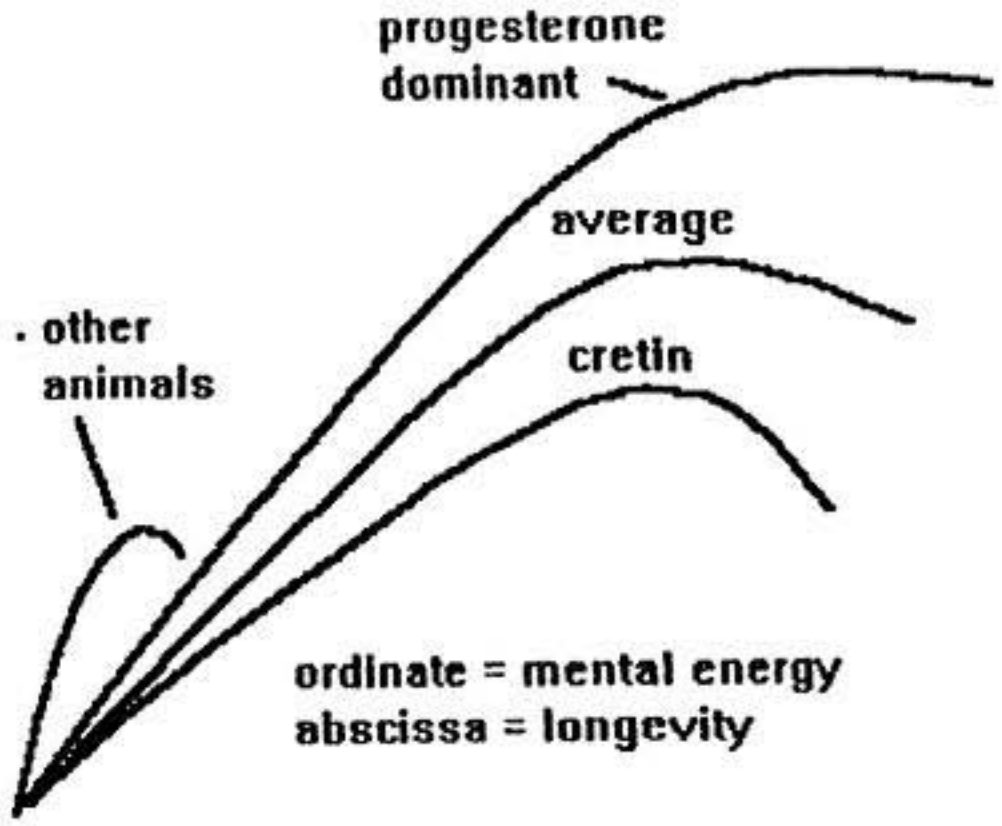
on intelligence, body proportions, and rate of aging, the genetics-reductionist school ignored them, and defined themselves as the only scientific school of biology.

ENERGY AND THE BRAIN

When I was a student of literature, I was interested in the apparent energy differences between different writers and different social groups. The literature of dissent (I wrote my master's thesis on William Blake) always reveals an abundance, or excess, of energy. I came to see literary "periods" or styles (classical, realist, Romantic, surrealist, etc.) as reflections of a society's energy and structure. As I followed this line of thinking about the function of language in society, and in the life of the individual, I saw that Blake's descriptions of his own use of images and symbols made sense in relation to brain physiology. Even attitudes toward mathematical concepts, theories of ideal languages, and "language philosophy" related strongly to the person's attitude toward authority, energy, the body, and the nature of consciousness.(2)

After I had spent a few years studying and teaching linguistics, I decided to study brain physiology. At that time, a group at the University of California had already found that freedom and stimulation caused a cumulative, transgenerational increase in the size of rats' brains. Continuing that work, Marion Diamond has found that pregnancy, or progesterone treatment increases brain size and inhibits the development of age pigment (suggesting that longevity might also be increased). In 1968, another group found that prenatal hormone treatment (causing increased production of progesterone) greatly increased the intelligence of rats. Several

researchers have shown that brain size relates strongly to both energy production and longevity. A graph (Figure 2) suggests how adaptive (mental) energy and longevity might relate.



At a certain stage of gestation, there are more than twice as many brain cells as there are at the time of birth, and it is likely that good conditions for the mother and fetus--adequate blood volume, oxygenation, glucose, progesterone (3), thyroid hormone, and absence of toxins and nutritional imbalances--can preserve some of the cells that would normally die. Since the brain and the liver regulate the amount of glucose and hormones in the body, the conditions under which those organs develop will very likely influence their later functioning, and account for some of the transgenerational effects that have been observed.

MECHANISMS OF AGING

As I became aware of the influences of hormones and the availability of energy on the development of the brain, and the

effects of the brain on aging (and became aware of the amount of dogma in the neuro-sciences), I began to work on the ways in which energy metabolism affects reproductive failure, especially in senescent decline of fertility. I hoped that working in a less dogmatic area of physiology would still allow me to get a better understanding of the organism in general, including the brain.

Professor Soderwall and his students at the University of Oregon had shown that the corpora lutea (areas in the ovary which mainly produce progesterone) appeared to fail in aging hamsters, and that vitamin E supplements could extend fertility by a significant amount. His group showed that "aged ova" were not responsible for infertility, but rather that the uterine environment was not suitable for implantation. Soderwall had also demonstrated that excess estrogen could cause failure of the pregnancy at any point, from failure of the embryo to implant, to resorption of the fetus at a late stage of pregnancy.

Although I had investigated the association of estrogen with cancer, and knew from my own experience with migraines that stress, diet and hormones interacted in powerful ways, when I began to investigate the oxidative metabolism of the uterus I didn't realize that it would involve a convergence of several of my main interests. I was familiar with Otto Warburg's famous idea that cancer is caused by a "respiratory defect," and I knew that aged tissue has a diminished respiratory capacity.

The text-books indicated that estrogen deficiency and "aged ova" were responsible for senescent infertility. (The origin of these ideas in a dogmatic matrix is another story which I have told elsewhere.) I found that the uterine endometrium of old animals often consumed oxygen at a high rate,

and showed other signs of being under the influence of excessive estrogen. As I tried to understand this, I saw that several things could contribute to a high rate of oxygen consumption. Either too much estrogen, or too little progesterone could have the same effect, since it is the ratio between these hormones which controls their effects. A vitamin E deficiency increases oxygen consumption, and too much unsaturated fat has the same effect. In a vitamin E deficiency, unsaturated oils are oxidized in a way that produces "age pigment," also called ceroid pigment or lipofuscin. This pigment consumes both oxygen and fuel, but produces no usable energy. Estrogen excess synergizes with a deficiency of vitamin E to intensify the formation of this pigment. Partly, this might be because estrogen is a powerful stimulant of iron absorption, and iron is involved in the peroxidation that produces the pigment. But low oxygen concentration is what causes the iron to become active in peroxidation, and estrogen acts in several ways to decrease the availability of oxygen. It appeared, therefore, that many of the features of aging resembled an estrogen excess, rather than estrogen deficiency.

The way in which estrogen prevents or terminates pregnancy seems to be by causing the uterus to consume oxygen at such a high rate that there is no oxygen available for the embryo, which has a high requirement for oxygen beginning on the day that it normally implants. The chronic or cumulative effects of estrogen, leading to formation of lipofuscin, happen to act in the same direction as estrogen itself, causing oxygen to be reduced, especially in the uterus, but in all other tissues, too (aging the whole organism). Estrogen excess can also destroy the corpora lutea, interfering with the production of progesterone. Progesterone's effect in pregnancy is to assure the availability of oxygen and nutrients for the embryo, but it also has the general effect of inhibiting the formation of lipofuscin,

and of other aging signs, by improving efficiency. (Progesterone is unusual among the anti-stress steroids in having no harmful side-effects.)

Although my work confirmed the other research that had been done in Soderwall's lab in the preceding 25 years, the idea that estrogen's influence appears to increase with aging, and even to contribute to the process of aging, was contrary to the doctrine that has been promoted by the pharmaceutical industry. Nevertheless, as I read more, I saw that there was really no evidence contrary to what I had seen in my own work. What existed was a web of interpretation which existed to sell estrogen treatments. Even the fact that estrogen causes abortion was "ignored," very consciously, until the industry had fabricated a more acceptable rationale with which to sell its "contraceptive" pills.

The idea of many factors acting in the same direction, and tending to have a cumulative effect, seemed to me to have a general biological significance. It seemed to be part of the answer to the question of what it is which is lost, or accumulated, during aging, which accounts for the decreased ability to adapt to the changing environment. It seemed to say something about the nature of Warburg's "respiratory defect" in cancer. The thyroid hormone, which governs respiration, is suppressed by estrogen, and by unsaturated fats. The wasteful metabolism of estrogen dominance tends to use up glucose, and is likely to activate the stress hormones, including cortisol. The main features of aging can be produced directly by administering excessive amounts of cortisol. These features include atrophy of skin, arteries, muscle, bone, immune system, and parts of the brain, loss of pigment (melanin), deposition of fat in certain areas, and slowed conduction velocity of nerves. The physiology of aging (especially reproductive aging) overlaps the physiology of stress.

LIFE-EXPECTANCY OF ADULTS

When there are sewers and clean water, the death rate of infants and children from infectious diseases isn't high, so the average age of the population increases as a larger percentage of those born live into old age. Increased use of birth control will also increase the average age of the population if fewer children are born each year. These changes in the birth rate and infant survival can happen at the same time that industrial pollution is causing chronic poisoning which shortens the lives of mature people.

To understand the effects of aging on the risk of human disease and death, we need information specifically about people who have reached a certain age. There are several organizations and individuals in the U.S. that have cleverly used "re-standardized" statistics to convince the public that cancer is being defeated, industrial pollution is harmless, sickness is caused by the victim's own irresponsible choices, and that our longevity has increased by several years in the last few decades. Old people are the most likely to die of cancer, and the cancer death rate for old people in the U.S. has been increasing in recent decades, as has the cancer death rate for the population in general. The life expectancy for older people in the U.S. has barely increased a year in recent decades. 2,000 years ago, the life-expectancy for older people seems to have been several years longer than it is now (Figure 3).

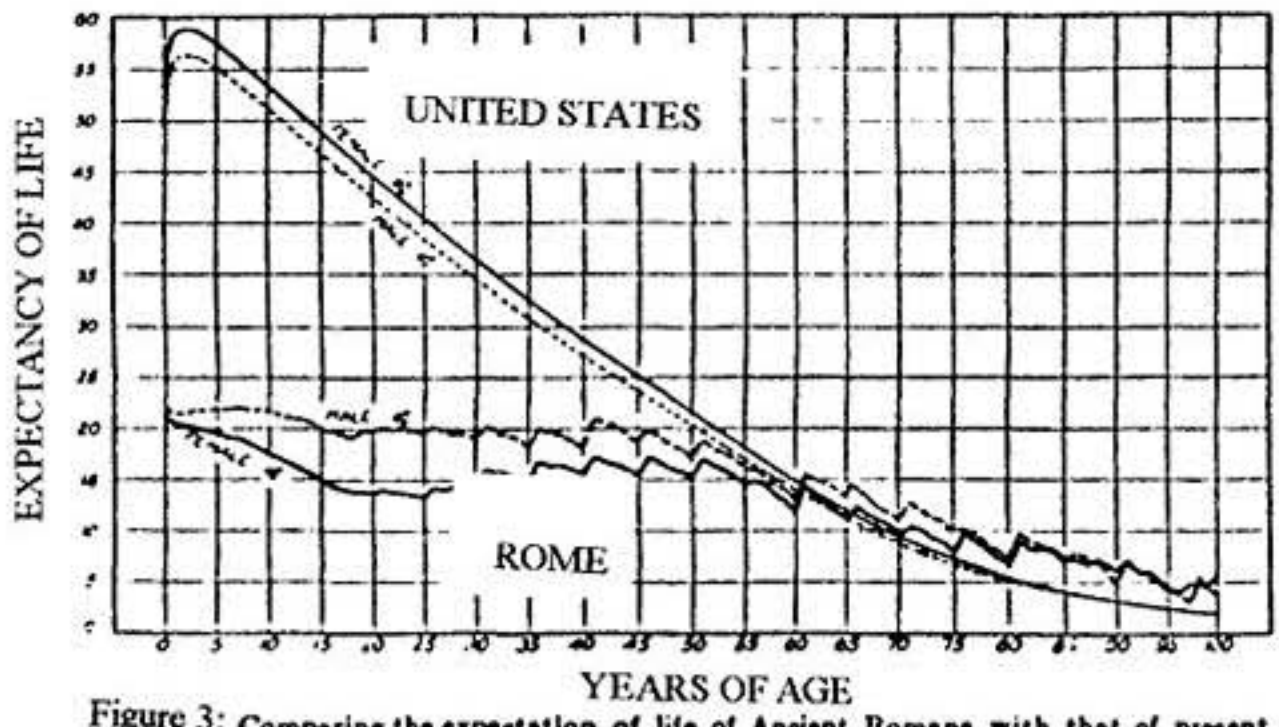


Figure 3: Comparing the expectation of life of Ancient Romans with that of present day Americans. Plotted from Macdonell's and Glover's data.

PUBERTY AND AGING

Many studies have demonstrated that puberty seems to trigger the mechanism of aging, and the idea of a "death hormone," located in the pituitary gland, has been suggested. (Figures 4 and 5.) Many degenerative diseases develop under

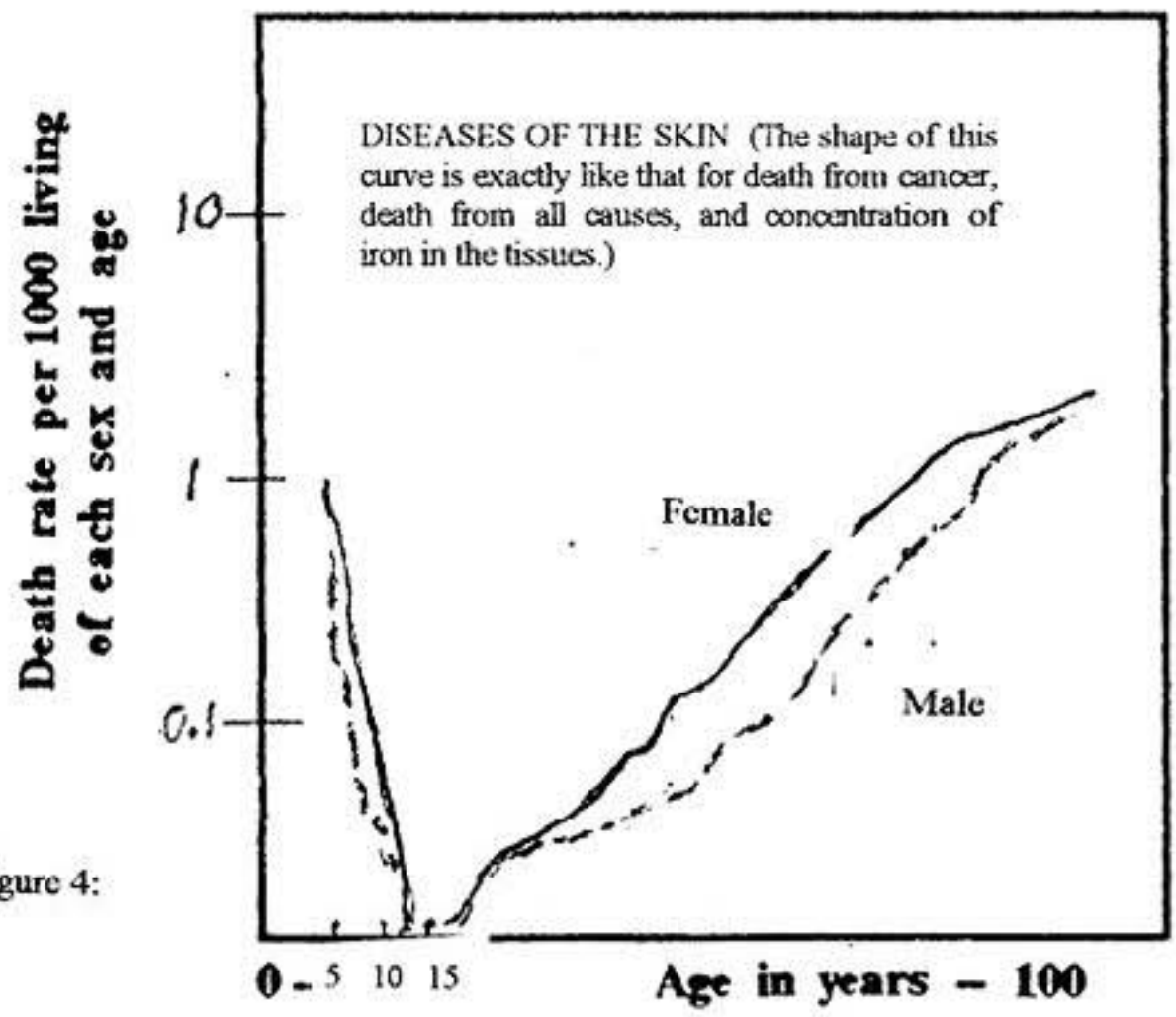


Figure 4:

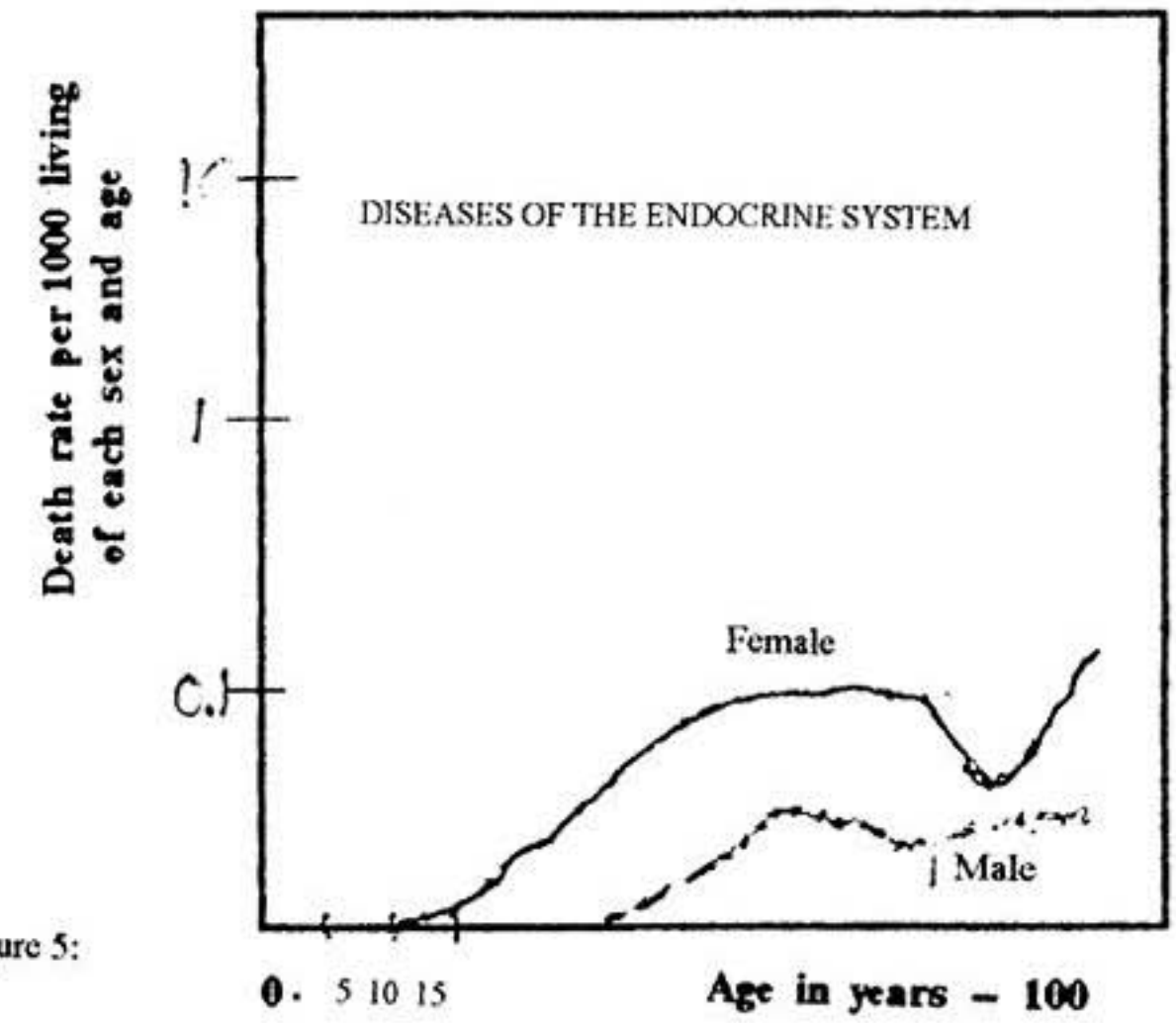


Figure 5:

the influence of excessive estrogen and cortisone (and as a result of the many metabolic changes which follow exposure to those hormones). Many of these diseases, especially those which appear after puberty and are more frequent in women, can be treated very effectively with the anti-estrogen and anti-stress hormones, such as progesterone.

Hans Selye pointed out that estrogen treatment mimics the first, "shock" phase of the stress reaction. An excess of estrogen (or any stressor) causes the pituitary to secrete prolactin and ACTH, and both of these hormones act on the ovaries to stop progesterone production, and contribute in many other ways to the process of atrophy. ACTH, of course, stimulates the secretion of cortisol. The removal of the pituitary obviously isn't a practical way to delay senescence, but protection against the "death hormones" can be achieved to some extent by altering the diet to minimize the effects of estrogen and cortisol.

Historical and demographic studies show that certain conditions affect the age at which puberty occurs. Ashley Montague has argued that we need more neoteny, that is, that we should try to preserve and to extend our youthful functions, because those are our most human qualities. If we can generalize from animal studies, delaying puberty could increase brain size and longevity, improve intelligence, decrease violence, and even make people physically more attractive (the "cute puppy" appearance is largely a matter of brain size in relation to the size of the face and body). I think this will be the next step in human evolution. Just as nurturing, stimulation, and freedom promote improvement in the function and structure of the brain, cruelty and oppression act in the opposite direction. If puberty is delayed, then the importance of a culture which supports curiosity, exploration, play and

sensuous pleasure seems obvious, so that biology and culture will be mutually supportive.

The physiological age of the parts of an organism depends in some way on the developmental stage of the whole organism. This contradicts the reductionists' idea that cells or tissues have an "intrinsic" lifespan which will cause them to deteriorate after a certain limited number of divisions. When pieces of breast tissue or skin were repeatedly transplanted from old animals to young animals of the same (syngeneic) strain, they were still in good condition after ten "life-times," and their survival was apparently limited only by the necessity of trimming them each time they were transferred, to make sure that no host tissue was transplanted with them. When old rats were grafted onto young rats, the old member of the pair lived to twice the expected age. Recently, young female mice were grafted onto old females, to investigate any hormonal factors in aging. The ovaries of the young animal appeared to age, and its production of progesterone decreased. That is, old tissue seems to become younger on young animals, and young tissue can be "aged" by association with an old animal.

This kind of evidence (and the simple observation that the cells in skin and intestine undergo thousands of divisions in an individual's life-time) strongly favors the idea that a systemic energy problem is involved in aging.

ENERGY AND EVOLUTION

V.I. Vernadsky believed that the earth's energy-exchange and substance-exchange processes were intensifying, and that the biosphere would undergo another major increase in its "metabolic rate," similar to that which appeared early in life's

development with photosynthesis. M.I. Budyko (in *Evolution of the Biosphere*, 1986) discusses the principle of "aromorphosis," in which the origin of higher types of animal is closely associated with the availability of larger amounts of energy in the environment, and with the appearance of new structures which made possible a higher energy level of activity and more complex interactions with the environment.(4) When vertebrates developed an effective method of heat regulation, they were able to considerably increase their use of energy. The move from water to land requires greater ability to use energy, as well as requiring new structures suitable to the new way of living.

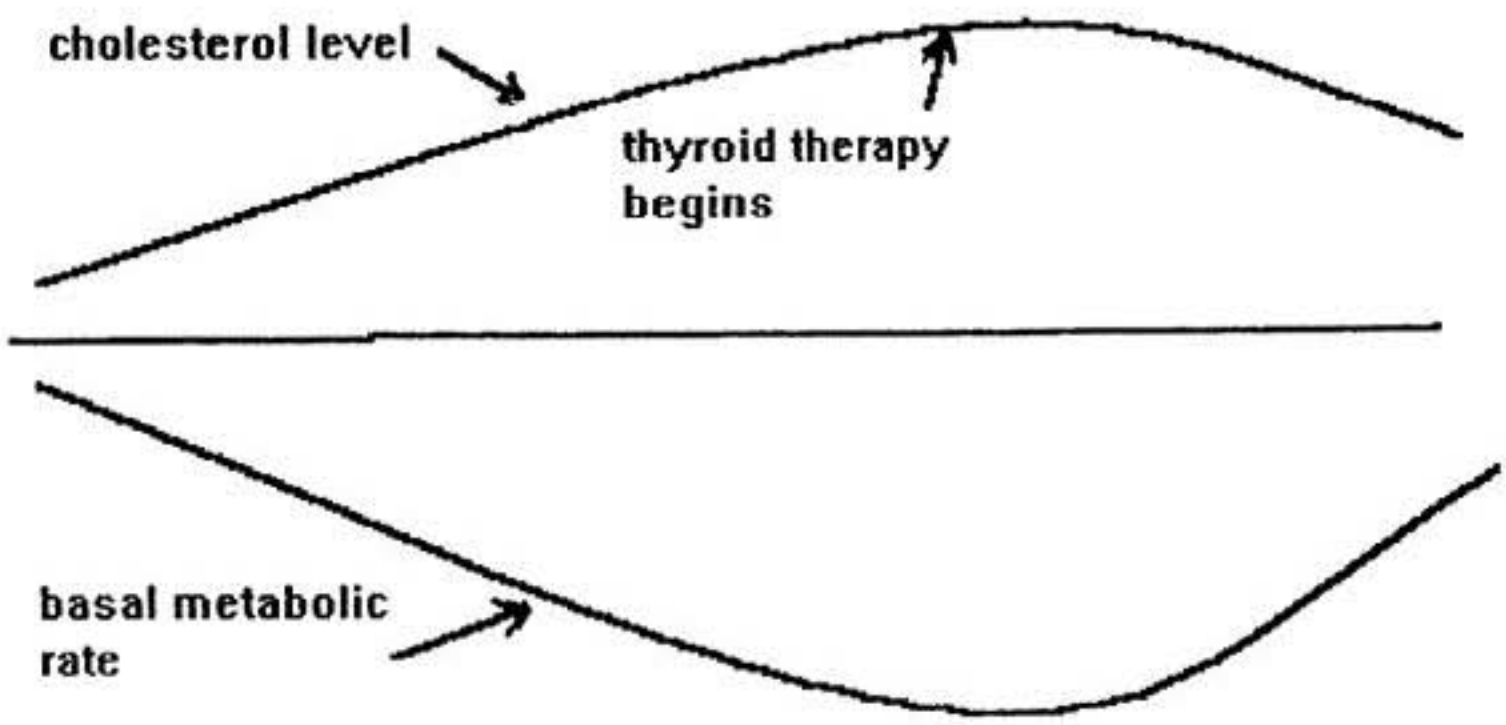
When mammals and birds achieved the ability to sustain a high metabolic rate by keeping their bodies at a steady, fairly high, temperature, their "food chain," based on photosynthesis, consisted of organisms that generally lived at a lower temperature.

Sugars, proteins, and the saturated fats produced by warm organisms can be eaten by warm-blooded animals with no particular side-effects.(5) Organisms that live at low temperatures, however, contain unsaturated fats. The consumption of large amounts of unsaturated fats lowers the metabolic rate, and accumulated unsaturated fats are susceptible to a spontaneous and toxic form of oxidation. (The toxic effects include damage to the respiratory apparatus and to the circulatory and immune systems, increased rate of aging, and cancer.)

These "low energy" foods in effect counteract the evolutionary achievement of a high metabolic rate. Several studies show that decreased consumption of unsaturated fats can delay puberty. Other studies show that an excess of unsaturated oil in the mother's diet can damage the development of the fetus's brain. The choice of foods which have less

unsaturated fat tends to reinforce the achievements of evolution.

The seed oil industry has created a national phobia about the consumption of saturated fats and cholesterol, but there is no basis for the idea that those foods should be avoided. People with hypothyroidism are susceptible to heart disease, but their elevated blood cholesterol becomes normal when their thyroid function is restored. (Figure 6) The body's highest concentration of cholesterol exists in the brain. The level of cholesterol in the blood strongly influences the production of the protective hormones, such as progesterone. The brain contains by far the body's highest concentration of these hormones.



Another energy-promoting factor is visible light. In the winter and at night the respiratory energy producing system is damaged, and the protective hormones decline, and the harmful stress hormones increase. The immune system becomes less active, and mortality increases.

Although ultraviolet light interacts with unsaturated fats in the skin to accelerate aging (E.R. Pinckney, *Medical Counterpoint*, Feb, 1973) and to produce cancer, ordinary visible light has several beneficial effects in animals. One effect is the "regeneration" of the enzyme SOD (superoxide dismutase), by causing its copper atom to be re-attached to the protein. Light also increases the activity of normal respiratory enzymes, and tends to normalize (or maximize) the production of hormones, including progesterone and thyroid.

Animal migration to reproduce in regions with longer days is a way to benefit from this energy-promoting action of light. In adult birds, the increase of hormones in the spring causes the growth of new brain cells in the area that controls their singing. (In humans, the space inside the cranium keeps increasing into old age, and the amount of DNA in the brain also keeps increasing with age, but it has been assumed that such changes in adult brains result from an increase in the size of nerve cells, and an increase in the number of connective tissue cells, rather than from a continuing increase in the number of nerve cells.) I would expect an increase in the temperature of the earth, and increased use of artificial light (or migration) to lead to a prolongation of youth and the development of better brains.

Many years ago, people talked about the tendency toward "cephalization" in evolution. That is the tendency to create a hierarchical organization, with the size and importance of the brain increasing with evolution. More recently, it was found that both the intensity and the efficiency of respiratory energy production in the brain increase with evolutionary level and with the degree of alertness.

Another seemingly directional tendency relating to energy production has to do with a non-random composition of the

DNA. Aerobic micro-organisms' DNA has a higher G+C (the bases guanine and cytosine) content than does that of anaerobes, and warm-blooded vertebrates have more G+C than do lower organisms, with the G+C content again corresponding to the amount of oxygen used. Although the full meaning of the G+C content isn't known, it is thought to affect the stability of the organism at various levels, and I suppose this would allow the organism to thrive at higher temperatures.

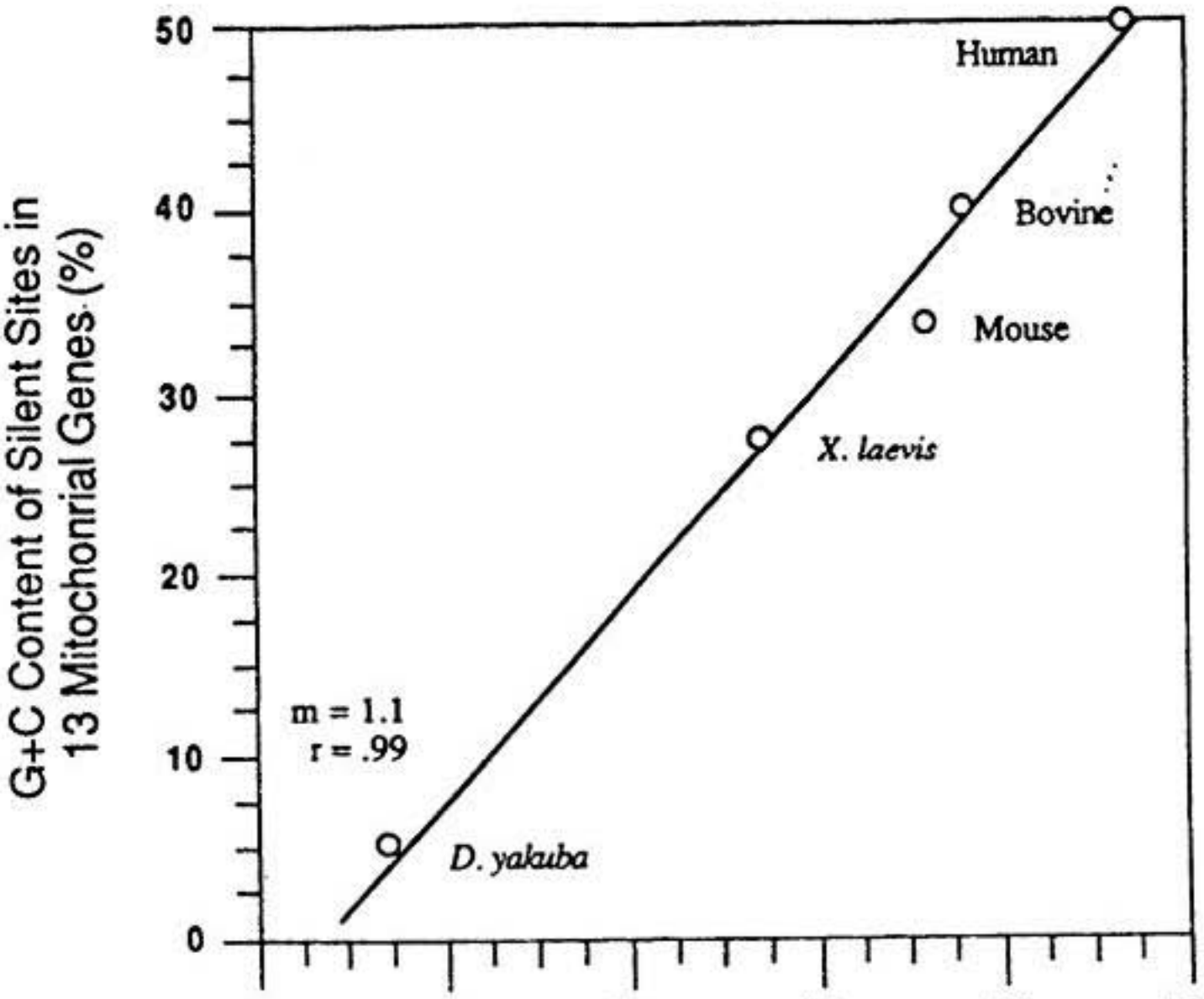


Figure 7: "Silent Nucleotide Substitution and G+C Content of some Mitochondrial and Bacterial Genes," T. H. Jukes and V. Bhushan, *Journal of Molecular Biology 24*, 39-44, 1966.

The association of G+C content with evolutionary level is interesting because the changes occur in "non-coding" DNA, where the ordinary kind of selection, involving "coded" proteins, isn't involved. The "isolation" of the genome, and the randomness of its changes, used to be at the core of genetics; I suspect this is why even most biologists aren't aware of this odd feature of DNA composition. The passage of time will allow people to disengage themselves from an embarrassing dogma. (Figure 7 shows the ascending G+C content for fruit fly, toad, mouse, cow, and human, in the DNA of the mitochondrion, where energy is produced.)

POLLUTION

Besides the distortion of our food supply by the propaganda of the seed oil industry, there is increasing contamination of our food supply by heavy metals. Lead, for instance, has been spread everywhere, largely as a result of its use in leaded gasoline. Food additives are often contaminated with heavy metals from the sulfuric acid used in their manufacture. Many people are aware of the famous experiments in which food restriction increased the longevity of animals, as if eating were toxic. But removing toxic heavy metals from the food, without restricting the amount of food eaten, has had the same life-extending effect in experimental animals.

When estrogen is elevated (as at puberty, or in pregnancy, or with medical estrogen treatment) the absorption of iron is stimulated. During aging, the body's load of iron increases, especially if there is a deficiency of copper, and the body's content of copper decreases with age. Copper is an essential component of cytochrome oxidase, which has the crucial last position in the mitochondrial respiratory system. Copper is a component of the cytoplasmic SOD enzyme, which decreases

with age. Ceruloplasmin, a major copper-containing protein, helps to keep iron in its safe oxidized form. Copper is involved in the production of melanin (itself an antioxidant) and elastin. The loss of melanin, elastin, and respiratory capacity, which is so characteristic of senescence, is also produced by excessive exposure to cortisol.

The protein, metallothionein, is rich in sulfhydryl groups, which bind heavy metals. It is assumed that this protein helps to detoxify and eliminate the toxic metals. This protein is induced by exposure to either a heavy metal or cortisol. A larger amount is produced in response to the combination of heavy metals and cortisol, than by either alone. Since copper, like the toxic metals cadmium, lead, mercury, and silver, reacts strongly with sulfhydryl groups, the body is likely to lose some copper when it is subjected to heavy metals or cortisol. I think this chronic loss of copper accounts for the obvious features of aging, such as loss of elasticity of the skin, lungs, and blood vessels, the depigmentation (demelanization) of skin, hair, and (in Parkinson's disease) substantia nigra, and for the decrease in respiratory capacity. The replacement of the copper by iron (and the loss of the copper-enzymes which protect against iron-catalyzed free radicals) probably accounts for the increased formation of lipofuscin during aging. When copper-dependent mitochondrial respiration fails, lipofuscin has the ability to sustain energy production through glycolysis (by keeping the coenzyme NAD, nicotinamide adenine dinucleotide, relatively oxidized), so it is possible that lipofuscin is a primitive sort of defense against stress.

In animals, copper supplementation can restore natural color to white hair, and in one experiment, it increased longevity. At present, there isn't enough knowledge about the safety of different ways of administering supplemental copper. It can be toxic, and it oxidizes other nutrients. Besides choosing

foods high in copper and low in iron and other heavy metals, other dietary choices which support thyroid function will tend to promote the retention of copper. Other dietary practices can minimize our production of cortisol (e.g., combining fruits and proteins, since protein foods lower blood sugar and stimulate the secretion of cortisol).

SELF-ORDERING PROCESSES

An old idea in our culture, which still inclines many people to a "billiard ball" conception of mechanistic causality, is that matter must be ordered "from outside." For Descartes, this involved a material world which lacks "secondary" qualities, i.e., every quality other than being present in space. That abstract world was supplemented by an utterly separate world of mind and spirit. Descartes' spirit has continued to live in many geneticists, who see "selection" as an ordering principle imposed upon a stupid sort of material substance, which can vary only randomly, by chance.

This genetic doctrine has a strong influence on medical thinking. Hundreds of diseases have been classified as "genetic diseases," and the idea is extended by showing an increased susceptibility among certain genetic tissue types even to germ-caused diseases and toxic sicknesses. Diabetes, allergies, arthritis, goiter, and myopia are often said to be "caused by genes," despite clear evidence for the involvement of the environment in producing them.

Several famous molecular biologists have been writing and lecturing about their idea that everything in our behavior and culture (including art, politics, and language) is specifically programmed by genes. (It would seem that I performed genetic surgery on one of these people, or caused him to mutate,

when I pointed out some glaring errors in his argument, and saw that he subsequently changed his claims.) Physical science provides a much richer picture of the qualities and potential of the material world than geneticists recognize. Even many physicists don't recognize the richness implied by the body of experimental results in their field. Many well known physical scientists have had relatively holistic attitudes (e.g., J.C. Bose, Michael Polanyi, B.V. Deryagin, Frederick Soddy, V.I. Vernadsky). A rich view of physics has much to offer to biology. However, when I say that a holistic view of biology is open to using physics and chemistry, as well as ecology, history, and cosmology, to achieve an adequate understanding, I should mention that there is a school of weird (immaterial and "quantum" centered) physics which is presenting itself as a holistic world-view. To them, I think Einstein's remark still applies: "You believe in a dice-playing God and I in perfect laws in the world of things existing as real objects. . . ." Elsewhere, Einstein observed that an object's fields amounted to an extension of its material substance, i.e., he preferred to materialize fields, rather than to dematerialize things, as some of the popular philosophers of physics do.(6)

The orderly, epitaxial growth of crystals has been shown to occur across the thickness of a plastic film. A detailed study of this sort of long-range ordering process was made by Alexander Rothen. He was able to demonstrate biologically specific adsorption at relatively great distances. Many other types of research in adsorption fields and long-range order make it clear that the interactions of atoms and molecules in cells needn't be governed by either direct contact or by random motion. When cell components are rearranged, they return to their normal position in relation to other components, revealing a great capacity for self-assembly or self-ordering.

The medical tradition of naturopathy recognizes a great capacity of the body for self-regulation and self-healing. I think these attitudes can be usefully expanded now, in the light of new knowledge about energy and structure. On the short time scale in which we think about the health of an individual, and on the transgenerational scale relating to having healthier, more intelligent children, and on the evolutionary time scale, I think we can see a tendency, not just to preserve homeostasis, but to move upward in energy and greater generality of structure and function. To provide more energy and scope for using it stimulates our ability to use energy meaningfully.

SOME IMPLICATIONS

There is considerable flexibility in living organisms, and in higher and lower levels of organization, and we can see some of the ways in which structures of different complexity accommodate themselves to the surrounding condition of energy and structure.

The conditions under which the brain develops, including gestational support and the later nutritional, hormonal, and behavioral conditions, the degree of stress and stimulation, contribute to the brain's structural complexity and metabolic energy use, and to the organism's ability to cope successfully with the environment.

Vicious circles of physiology often stabilize an organism on a low energy level, which may involve disease or rapid aging.

The existence of a few systems of positive feedback (self stimulation), however, indicates that in our fundamental structure we are biased in an expansive, upward direction. Progesterone (and its precursors, pregnenolone and cholesterol) and thyroid hormones participate in some of the important

positive feedback systems, involving energy production, stress resistance, and brain growth.

In therapy and in everyday living we can try to protect and promote our energy-producing and energy-using systems by seeking the stimulation, the conditions of light and temperature, and the foods that are appropriate for our evolutionary level.

NOTES:

1) Resonance has to do with approximately simultaneous interactions between energy and matter, and hysteresis, with the lingering effects of earlier interactions of energy and matter.

2) I circulated a questionnaire in 1957 among college students of various nationalities and classes. My conclusions suggested that the contemporary white male Western abstract personality was dysadaptive, in the sense that many vital abilities or capacities were undeveloped or suppressed.

3) Progesterone is one of the factors in a "chemically defined" medium for the growth of nerve cells in culture. The others are insulin, transferrin, selenite, and putrescine.

4) Budyko's idea that energy drives the biosphere is unfamiliar to our Anglo-American culture, which has tried to think of everything, even the weather (and especially evolution) in terms of mechanics, inertia, statistics, and hydrodynamics. There is a resistance to the idea of directional, dynamic self-governing systems. The sun's energy for photosynthesis tends to be kept in a background role.

5) "Warm organisms" means either organisms that keep warm by internal heat production and temperature regulation

or organisms that are warm because they are kept warm by the environment.

6) Paul Forman, in an article in *Studies in the History of Science*, gives some valuable historical information on the social factors involved in Germany of the 1920's, when physics' departure from the world of real objects became so conspicuous.

CHAPTER 2

ANOTHER VIEW OF EVOLUTION

A few people have pointed out that order can't be expected to emerge from disorder, even "if you wait long enough," unless an ordering principle, a "formative tendency," is present in the starting situation. "Chaos," then, would be described as "potential," and the development of organization would be more like a snowball rolling downhill, than like the step-by-step preservation of "random variations" over an almost infinitely long time scale. Our knowledge of ourselves, and our sense of the meaning of life, are influenced by the answer to this basic question about the nature of order, and of the origin of life.

When complex organic compounds were found in petroleum, some people argued that this was evidence that the petroleum was the residue of dead organisms, that had seeped into porous geological formations. Another view is that petroleum was directly created by the earth, and that life is a parallel creation.

In 1859, the year Darwin published his famous book, the first oil well was drilled in Pennsylvania, and chemists began to study petroleum with increased interest. When high-carbon iron is dissolved in hydrochloric acid, an oil appears on the surface of the acid. Mendeleev noticed that it resembled natural petroleum, so he gave samples to people who were familiar with petroleum from different parts of the world. All identified its smell as that of petroleum, and some even thought they could identify the region it came from.(1)

Mendeleev and others proposed that molten metals deep in the earth might interact with the carbon present in minerals to create petroleum.

Recently, Gustaf Arrhenius at the Scripps Institute of Oceanography has been studying the ability of iron carbonates to produce organic compounds. I think the gap of 100 years between this work and the ideas of Mendeleev and his contemporaries is the result of a dominant habit of thought which sees the world as an inhospitable place, in which life is a great improbability that came into existence only with great difficulty. The famous Crick, for example, suggested that life had to originate elsewhere, and arrived on earth as a truly alien space-traveler. The thought that life forms might just sort of gush up out of the earth in volcanic regions makes it all seem too easy; where might it lead if people started believing that life could originate without a struggle for existence?

Several years ago, Sidney Fox demonstrated that amino acids placed on a hot volcanic rock spontaneously formed into proteins, and that these proteins had some enzyme-like catalytic action. Adding a little water, the proteins spontaneously formed small self-reproducing spheres, just the size of bacteria. One of their enzyme-like actions was the ability to synthesize gene-like chains from suitable precursor molecules.

Explorations of the deep ocean floor, far below the level at which life should exist, because of the absence of light, revealed worm-like organisms. Further study showed that the worms live on bacteria, which in turn live on volcanic emissions rising through the ocean floor. If volcanic processes created life forms, and can even provide their food, then we don't have to imagine that green plants necessarily evolved before animals.

Oxidants(2) are emitted by volcanism, and there are heme-like porphyrin molecules in petroleum which can catalyze respiration-like reactions. While molecular oxygen is now our most important electron acceptor (oxidant), other substances could have had a similar function. And, since volcanos emit both oxidants and reductants (depending on temperature and other conditions) we shouldn't blindly accept the doctrine that life originated in a "reducing atmosphere."(3) Since the reactions which produce petroleum-like hydrocarbons do not produce carbohydrates, we might want to investigate the possibility that carbohydrates are the product of a primitive type of metabolism.

Several things look different when we consider the possibility of a volcanic origin for life. For example, there is a suggestion that life originated in abundance, in an environment rich, at least locally, in complex organic molecules, rather than in occasional puffs of molecules generated by lightning or dissolving slowly out of a meteorite. And the thought that life is truly geological, and is an expression of our planet's nature, might make us feel more at home, and nurtured.

If we think of life, already complex and respiring, moving into the light and adapting to a new system in which carbon dioxide is captured from the environment for new syntheses, we are likely to ask a different set of biochemical and bioenergetic questions. Detoxifying systems, that would have evolved to protect respiration from compounds such as ammonia, cyanide, and carbon monoxide, might have been the first systems to make use of light. Evolution of these systems might have led into photosynthesis. If this is true, then the theoretical and chemical study of the origin of life might give us some clues to the nature of the biological rhythms based on the cycle of day and night.

Several people have written about the idea of a "noosphere." Pierre Teilhard de Chardin, in *The Human Phenomenon,* used the term coined by Edouard Le Roy. V. I. Vernadsky, in *Biogeochemical Essays,* developed the concept in relation to the principles of biogeochemistry. Vernadsky saw the noosphere as a stage in the natural geological development of the earth. He suggested that the various stages and aspects of the earth, the lithosphere, the hydrosphere, the atmosphere, the biosphere, will be followed by a stage in which a highly developed human society will recognize its place in the world and with understanding will guide the preservation and development of the natural system.

This is not exactly the same as the "Gaia hypothesis," which sees the earth as an organism-like self-regulating system, since the people who talk about the noosphere idea recognize the damage that human life has already done to the biosphere, and emphasize that the course of human civilization will be crucial in the fate of the earth.

If we proceed blindly with aimless industrialization, deforestation, destructive agricultural practices and militarism, the entire biosphere could be destroyed, possibly ending the earth's progress forever. But if civilization proceeds toward an understanding that the world is in development, we might find our place in this developmental process. If this happens, the earth will be entering a new energy level, analogous to the earlier appearance of photosynthesis. As we build our understanding we can increasingly think of our consciousness as a geological force.

During the Second World War, Vernadsky wrote: "I look at everything from the point of view of the noosphere and I think that in the wind and storm, in the horror and ordeal, a wonderful new future is being spontaneously born."

NOTES:

1. P. N. Kropotkin, "D. I. Mendeleev's hypothesis on the inorganic origin of petroleum and its modern scientific development," *Mendeleev Chemistry Journal 31*(5), page 1, 1986.

2. Many of the conditions that exist in volcanos are able to generate molecular oxygen, e.g., heating metal oxides, oxy-acids and oxy-salts, adding chlorine to a lime solution, or combining chlorine and steam at high temperature. If released in explosions, the molecular oxygen could be over-looked.

3. The "argument" that life originated in a reducing atmosphere is that ultraviolet light causes that kind of atmosphere to form many organic compounds; oxygen would form ozone, blocking the ultraviolet radiation. If ultraviolet light created life, oxygen must have been absent. If something other than ultraviolet light produced the complex organic molecules, the presence of oxygen would simply have had the same protective effect it now has.

CHAPTER 3

VERNADSKY'S HOLISTIC SCIENCE

Increasingly in the last decade, people in the Soviet Union who are interested in perestroika and an alternative world view have been thinking about V. I. Vernadsky and his work. Ecologists and conservationists in that country have found that his picture of the world offers an approach to the unity of life and its environment which is both practical and inspiring. While it initially sounds like a strange thing to say, Vernadsky's work made a real place for human consciousness and history in science by using simple physical concepts such as mass, energy, and rates of change, for approaching the biosphere. By examining the limits set by space and the flow of energy from the sun and the earth, Vernadsky was led to propose some simple laws of biogeochemistry, for example that the migration of chemical elements tends towards a maximum. Within this framework, he saw that the intensity of biological reproduction and metabolism and the degree of biological organization have orderly and lawful interrelations, and that human culture and consciousness participate in these natural relationships and processes. Vernadsky described his view as "cosmic realism," a phrase that had also been used by Mendeleev.

As a student, Vernadsky (1863-1945) was drawn toward both history and mathematics, and he read widely in philosophy and religion, including Plato, Aristotle, and Hinduism. After studying with Dokuchaev (who has been described as the pioneer of ecology because of his study of the interaction of biological and geological factors in the formation of soil),

Vernadsky studied in Germany and France. It seems that he sought out the best minds and strongest personalities of the time, in many branches of knowledge. He knew the Curies, Hans Driesch (a student of Haeckel, the Darwinist; Driesch is known as a vitalist), Sechenov, Le Chatelier, Mendeleev, and Tolstoy, and was able to integrate their perceptions into his view.

For example, he wrote "I think that the teaching of Tolstoy is much deeper than I first thought. This depth consists in his view that the basis of life is the search for truth, and that the real task is to tell this truth without any retreats," and he described Tolstoy as an accumulator of the energy of human consciousness.

Tolstoy's moral thought was paralleled by Vernadsky's perception of unity, in which humans, as part of a cycle of transformations, have an obligation to think and act for the good of the planet. The creation and preservation of culture and human consciousness are given a central place in Vernadsky's view, but not at the expense of anything else in the world: Consciousness is needed by all of humanity, for the good of the world.

In 1922 Vernadsky lectured in Paris on biogeochemistry and on the place of consciousness in the history of the earth. These ideas were summarized in his 1926 book *The Biosphere*. He tried to get support in the United States to start a laboratory for the study of biogeochemistry, but his friend E. S. Dana at Yale was apparently the only American interested in the subject. The chairman of the chemistry department at Stanford said that the subject "hardly deserves the attention he would give it," and the proposal was also rejected by the Carnegie Institution, the National Research Council, and the British Association for the Advancement of Science.

Although many of Vernadsky's concrete discoveries have been independently rediscovered in the United States, his name seldom appears in American books on geology or ecology. I think this is because of his basic belief that nature is not ruled by accident. "Earth's structure is a harmonious integration of parts that must be studied as an indivisible mechanism. . . . Creatures on earth are the fruit of a long and complicated mechanism in which it is known that fixed laws apply and chance does not exist."

The idealization of randomness in German and Anglo-American science makes it hard even now to discuss physical and biological approaches which emphasize order, lawfulness, and directional transformations. Like Le Chatelier's ideas in physical chemistry, which were very influential in Vernadsky's thinking, the idea of a principle of "stability" which leads spontaneously to increased complexity and order in a system, is a little too alien to be received easily in our culture. Ilya Prigogine's work in this area is probably changing the atmosphere a little.

Unfortunately, even when there are systematic observations of the appearance of structure out of relative disorder, there is in the United States a preference to attribute the appearance of order to "chaotic" processes, and to argue from the "logic of chaos" that the future is absolutely unforeseeable, and that the world is chaotic rather than lawful. (If there is any significant chaos in this new doctrine, I think it is primarily in the terminology and in the illogical conclusions of some of its proponents.)

To Vernadsky, the world is lawful. His view of life as an active mass, a form of matter which must be understood quantitatively, "a whirlwind of molecules," acting on its surroundings, led him to think in terms of the rate of migration of

atoms through this active mass. With this view, inert atoms become active, while active atoms become inert, depending on their situation.

This idea of the "history of an atom" is perfectly natural from the "cosmic realist" point of view, but it leads to questions that just don't occur to a person who usually thinks of atoms as statistical and anonymous identities. His first biogeochemical law, that the migration of atoms tends toward a maximum, is obvious to anyone who thinks about it, and it is an obvious parallel to Le Chatelier's principle of equilibrium. Once that principle is accepted, and if life is seen as part of nature, then Vernadsky's second law, that evolution will produce species which maximize the migration of chemical elements, follows naturally.

But this requires thinking about the biosphere as a system which is driven by energy from the sun, and this context isn't habitual for evolutionists. Vernadsky said that his second biogeochemical principle "shows, in a manner as precise as the corresponding principles in mechanics and physical chemistry, the direction in which the processes of evolution must proceed, namely, in the direction of increasing consciousness and thought, and of forms having greater and greater influence on their surroundings."

Teilhard de Chardin got his idea of the Noosphere from Vernadsky's work. Many people prefer to see the idea of consciousness' having a meaningful and central place in evolution as exclusively a religious idea. However, from Vernadsky's perspective it can be derived from seeing life in physical and chemical terms. To make the implications of the idea clearer, it might be useful to apply it to some contemporary scientific questions, which could range from the origin of life, to the optimization of farming and dietary practices.

CHAPTER 4

THE CENTRALITY OF ANTICIPATION

"One gathers that the period of youth among mammals is not essentially recapitulatory but rather adaptive and anticipatory."

P.E. Davidson, in *The Recapitulatory Theory and Human Infancy*, Columbia University Press, 1914.

Energy flows through all systems, and the flow of energy leaves a residue of structure. In the 1960's and early 1970's, I made many "model" systems of the chemistry of respiration, trying to get perspectives on the meaning of biological respiration.

One of my experiments, in 1971, involved ascorbic acid, hydrogen peroxide, iodine, and copper. Every few seconds, the mixture alternately changed color and emitted puffs of gas; this is called an oscillating reaction, or a Belousov-Zhabotinsky reaction. This made me realize that "structure building" can involve the dimension of time, in a way more interesting than the simple dissipation of energy over time. When starting at a point, an oscillating reaction of this sort can generate interesting ring and spiral structures in space.

I see the interaction between the flow of energy (e.g., between a sugar and oxygen) and the structure as one in which the flow is retarded by the structure, and used by the structure, in maintaining and complexifying itself. (Another way of looking at this is that if energy can do something, it does

something; and what it does is to build structure. The life structure is a kind of energy charge, but the important thing is the spontaneous nature of the interactions, in the presence of an energy supply.) The chemical nature of the energy source (and of the energy "sink," which is usually oxygen) influences the nature of the structure-building.

A point made by O. Warburg and A. Szent-Gyorgyi and others is that there is an important difference between the energy provided by glycolysis and that provided by mitochondrial respiration. They felt that glycolysis was a more primitive form of energy production, and supported only primitive function and cell division, while the more efficient respiration supported cell differentiation and complex functioning.

Warburg thought that localization of mitochondria within cells could explain the special effects of respiratory energy, while Szent-Gyorgyi suspected that respiration more directly held the structural proteins of the cell in a special electronic state. It is now recognized that the localization of mitochondria within a cell creates an energy (ATP) gradient within the cell. (There has been a dogmatic disbelief in such gradients.) And, for example, the polyamines, which are associated with an increased rate of cell division, appear to shift cell metabolism away from respiration, toward glycolysis. The nature of the energy source seems to be more important than many biologists have thought.

Various hormones involved in adaptation and reproduction modulate the balance between glycolysis and respiration. Elsewhere (e.g., *J. Orthomol. Psych.*, 1975) I have discussed the hormone-like properties of various nutrients. In the 1930's, it was pointed out that all of the changes produced in rats by a diet lacking the "essential fatty acids" were the same

as the changes occurring in hyperthyroidism. Parallel to the balance (or antagonism) between opposing hormones, there seems to be some sort of balance and opposition between different sorts of food energy.

The structural and functional repercussions of different dietary energy sources are complex, and I plan to discuss some of them soon in more detail, but there is some evidence for a relatively simple sort of absorptive or solubility compatibility between the cell substance in a given energy state, and the fuel molecules preferred by that state. Conceivably, this could account for the apparent "directed mutations" in the ability of microorganisms to use new substances for foods, observed by C. C. Lindegren, J. Cairns, and others. In adaptation to foods which are actually present, no anticipation is required, but only a sort of structural accommodation.

When the availability of food changes according to a daily cycle of light and dark, there is an adjustment of the metabolism involving many hormones, and an adjustment of nervous function, to protect against stress (Figure 1). Learning is involved, in the sense that a cyclic repetition is anticipated even by "simple" organisms. In humans and other mammals, there is the "dawn phenomenon," in which blood sugar rises to daytime levels before sunrise.

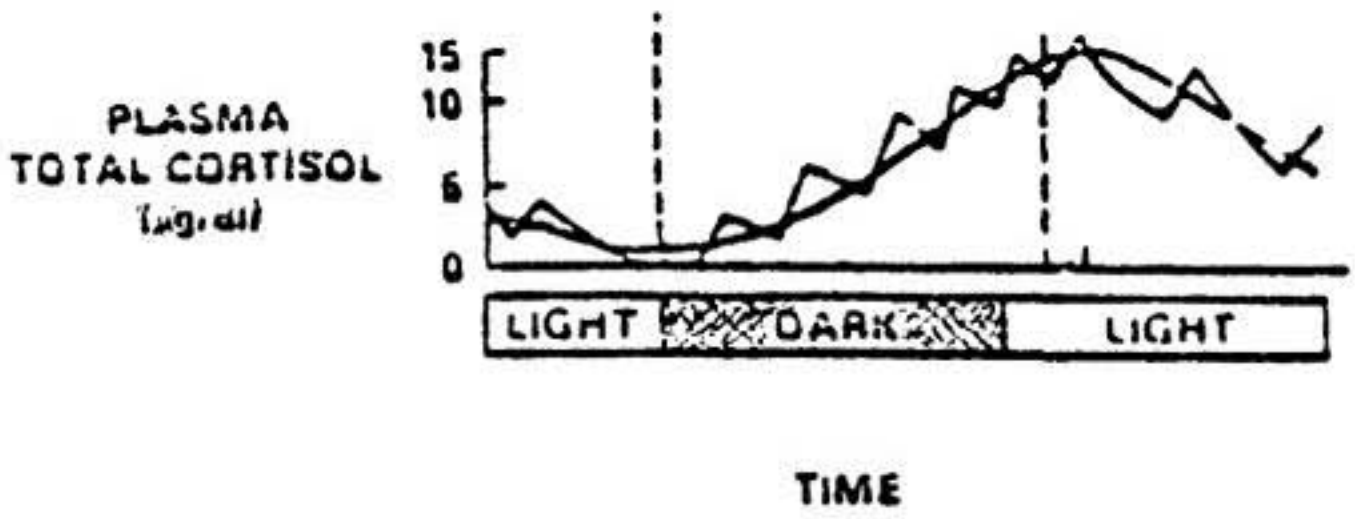


Fig. 1 - Blood cortisol rising during the night.

When food is abundant during pregnancy, and when the environment is not stressful, the brain of the fetus grows at a faster rate than in cases in which the pregnancy is affected by malnutrition or stress. Since the brain is a metabolically expensive organ, and since a larger brain tends to correspond to a higher metabolic rate of the entire organism, it appears that the developing fetus is anticipating a lifetime of relative abundance of food when it is well nourished in the uterus, and when it is exposed to less cortisol and more progesterone.

In evolution, the tendency toward dominance of the head (cephalization) in animals overlaps with another tendency (known in plants too) called juvenilization, pedomorphism, or neoteny, in which an early stage of the organism's development, the juvenile stage, is preserved for longer and longer periods in the descendants, eventually becoming the normal adult type. Baby apes resemble humans, in body proportions and behavior, much more than the adult apes do. The infant represents our evolutionary future.

Embryologists have observed that "ontogeny recapitulates phylogeny," that is, that early in development, mammals go through stages that resemble fish and reptiles. But I have always been intrigued by the fact that the same trend which can be seen going back from the adult to the infant--i.e., increasing of the brain-to-body ratio--can be seen to continue from the infant back to the embryo, at about the second month or seventh week of development. That is, the first few weeks of ontogeny recapitulate phylogeny, but then ontogeny also *anticipates* a phylogeny that hasn't been yet (Figure 2).

If the physical/chemical structures which retard the flow of energy, and complexify with it, accommodating themselves to it, reflect past and present conditions and types of energy source and energy sink, then presumably different geological

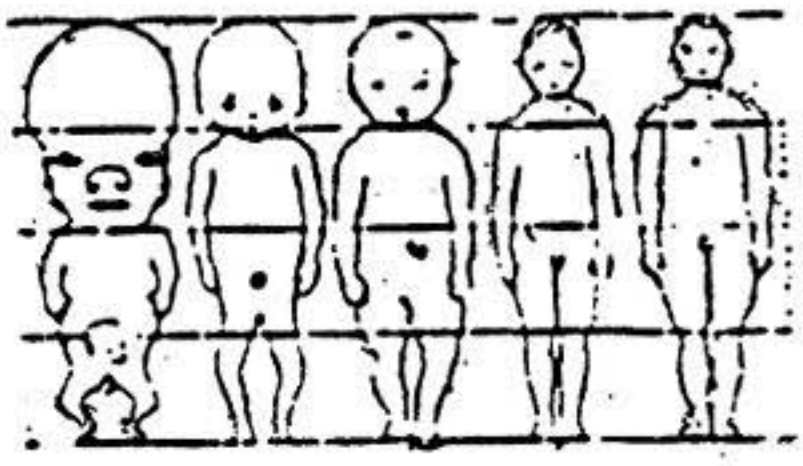


Fig. 2 - Ontogeny may anticipate phylogeny.

phases would be suitably associated with different anatomies and physiologies. The extremely favorable energy relationships which exist in the early embryo (which is very small in relation to its supply of energy) appear to support a certain structural relationship, which sketches out the structural-functional possibilities for the future, when our environmental energy resources might be richer.

NOTES:

The term "aromorphosis" has been applied to the sudden appearance of a new biological form, when energetic conditions are suitable (e.g., M. I. Budyko, *Evolution of the Biosphere*, 1986). Pedomorphosis, or juvenilization, can be thought of as the "aromorphic" response to an environment (or niche) which is becoming more nurturing: the infantile form, which requires nurturing, persists to take advantage of the richer, more energetic environment. V. I. Vernadsky and Ilya Prigogine each worked out some important parts of the theory describing the emergence of order out of disorder. F. D. Peat outlines Prigogine's ideas in *Synchronicity* (Bantam Books, 1987).

Each stage of evolutionary history has its characteristic metabolic chemistry. By protecting and promoting mitochondrial respiration we are contributing to our own evolution. (More on this subject appears in "Youth, Energy and Regeneration" and "The Life of Nature".)

*Le Chatelier's principle, that a system adjusts in ways which restore a disturbed equilibrium, is behind this idea. Every part of the flow can be seen as a disequilibrium, and the complexification of the structure tends to absorb the disturbing energy.

Referring specifically to the heart muscle, Szent-Gyorgyi said "function builds structure." Generalized principles of stability will illuminate the life processes in which stimulation produces growth and adaptation. Much of the needed knowledge already exists in a fragmented way.

A proposed law of aromorphosis: that the retardation of the flow of energy in living systems tends toward a maximum; in animals, this would imply a trend toward larger-brained, longer-lived, and probably warmer animals, having a higher energy charge.

CHAPTER 5

THE LIFE OF NATURE

"Then tell me, what is the material world, and is it dead?" He, laughing, answer'd: "I will write a book on leaves of flowers, if you will feed me on love-thoughts & give me now and then A cup of sparkling poetic fancies; so, when I am tipsie, I'll sing to you to this soft lute, and shew you all alive The world, where every particle of dust breathes forth its joy."

W. Blake (1794)

"If this were an entirely scientific matter, there is little doubt from the evidence that the case for a fundamentally biological universe would be regarded as substantially proven. The reason why the scientific community passionately resists this conclusion is that biological systems are teleological, which is to say purposive. And if we admit the universe to be inhabited by a vast number of purposive components then the thought cannot be far away that perhaps the Universe itself might be purposive...."

F. Hoyle (1989)

To read either poetry or "scientific" writing, it is useful to know what was going on in the writer's life. For example, if you know that Albert Einstein's family's business was ruined by the German electric-machine monopoly, his attitude toward the German-dominated physics establishment and its ideas will be seen in that context. The nature of

communication and of meaning itself makes a certain consideration ("ad hominem") of the communicator's general attitudes necessary for a clear and full understanding. Einstein explicitly recognized this situation when he said that a person's life can't be separated from the person's hypothesis.

To be valid and useful, a hypothesis must coincide closely with the facts, but that is only a minimum requirement. It must also be general enough to matter, to mean something, but that still isn't enough: It shouldn't be deceptive or propagandistic, and ideally it shouldn't be misleading in any way, for example by omission and by exclusion.

The dean of the Yale school of medicine said it wasn't proper for me to think that his school's research conclusions on the safety of Premarin could be influenced by a gift of a large amount of money from Ayerst (the makers of that ultra-lucrative product), but he refused to tell me how much money was involved. Big money from every major industry has corrupted our scientific culture, and it is important that we consider the scientific alternatives.

The links between Premarin and the Theory of a Dead Universe are not obvious, unless you think about them. Our product-oriented medical culture is strengthening the idea of the pathogen-destroying magic bullet, because magic bullets can be profitably sold and administered. The idea that the patient is a self-healing, self-organizing kind of being is unpopular with the medical business, because they have no investment in the providing of healthful environments: Clean air, clean water, clean food, safe work, good housing.

The "genetic defect" theory of disease holds the promise of a gene-implant for every problem. Interestingly, the people who point out that "thousands of genetic diseases are now known" neglect to mention that the "scientific literature"

supporting their claim is infinitely more "anecdotal" than the despised "anecdotal" support for the various unofficial remedies that are so offensive to the medical establishment. A doctor sees three people in a family with muscle twitches, and a Latin-named Twitchy Muscle Syndrome with dominant Mendelian inheritance enters the scientific literature. In thousands of such publications, the possibility of nutritional deficiencies and exposure to toxins isn't investigated, because there is such eagerness to recognize a new genetic defect.

There is a mystique in our scientific culture called Reductionism. It reduces the explanation for something to a description of its parts, and the ways the parts interact. A relatively small number of "elements" and "laws" are used to explain a great range of specific phenomena. My favorite formulation of the reductionist attitude is that of the famous Mr. Crick: What else is there but atoms?

The reason I call Reductionism a mystique is that its proponents feel it is so clear and obvious that they don't have to bother with philosophical complexity. They, in that sense, are the Fundamentalists of the 20th century. Although they emphasize the importance of analysis, formal reasoning, mathematics, and quantification, they are not interested in examining the philosophical basis of their methods, except occasionally to say something like "the scientific method has been proven scientifically."

Sanity itself requires that we not confuse our wishes, assumptions, methods, and ideas with the world that we are trying to understand. If our method determines our conclusions we are closer to theology than to science, and that is how many "scientists" prefer it.

An inference that something is generally true, based on some specific examples, is a matter of judgment, rather than

of formal logic. Different people may draw different inferences. An intelligent hypothesis is based on a lifetime of intelligent inferences. The element of judgment in choosing a hypothesis leads some people to suggest that there is an arbitrariness or even randomness to the choice of hypotheses. If we acknowledge clearly that our choice of hypothesis is a matter of our best judgment, there is no problem, because the virtue of science is in putting hypotheses to various tests, which will eventually eliminate the most mistaken ones. When we make specific formal deductions from a hypothesis we reveal its implications and look for ways to test these implications.

It is in the nature of formal reasoning that we can deduce specific details from something more general, but that we can't formally deduce something more general from specific things. This is where reductionism uses its method to impose a conclusion about the nature of the world.

The reductionism which says that physics can explain everything, because everything is composed of "these basic particles, according to fundamental laws of interaction," forces itself into asserting that the many forms of life can be deduced from the general laws of physics, and that the varied and specific forms of organisms represent the interaction through time of chance events (in the genes) with the determining forces of the environment. The mode of explanation leads to the content of the science. The nature of formal logic, proceeding from the parts, requires that the whole be explainable in terms of its parts. If the trick that explains the whole can be found in the nature of the parts, there is no problem, but problems arise when the reductionist claims that we already have the kind of knowledge of the parts that can adequately explain the whole. In this sense, biology is seen as less

general than physics, and physics contains an adequate explanation for biology.

A story from a 1915 physics conference in Berlin will illustrate how the desire to explain things in terms of the parts can create problems even within physics itself (and its traditional subject matter). Michael Polanyi, a Hungarian, found that there was a simple formula that accurately described the adsorption of gas molecules on charcoal, at different pressures, in terms of an "adsorption potential" extending through space, which allows various layers of gas molecules to condense on top of previously adsorbed layers, as the pressure is increased.

The famous German physicists at the meeting pointed out that their modern knowledge of the electrical nature of matter made it evident that the first layer of molecules would neutralize the adsorbing force of the charcoal, and that it was only because Polanyi was working in a backward country that be thought an adsorption "potential" could somehow reach out into space through a layer of molecules to pull in more molecules.

Around 1930, Langmuir proposed his relatively complex multilayer adsorption theory, but by then Polanyi's more elegant adsorption isotherm was remembered only as the embarrassing "mistake" of a young man from a backward country. (We should also remember that the "modern" notion of the electrical nature of matter formed the very basis for such work as the theory of the photoelectric effect, which had such importance in the development of the quantum theory. If atoms aren't the discrete little packets they were thought to be around the turn of the century, then the need for discrete little packets of energy isn't as evident as it seemed then. Polanyi's other projects turned up other aspects of matter that weren't acceptable to the physics of that time.)

If the world's best physicists and chemists used a reductionist approach to block the development of an important branch of physics, it is clear how the approach can obstruct the development of ideas in more complex fields, such as biology and cosmology. If the Germans had taken Polanyi's adsorption work more seriously, they would have had to revise their rigid and mistaken ideas about "the electrical nature of matter." A higher level of organization of substance (as in Polanyi's experiment) can, if insightfully described, provide new knowledge about the nature of the "parts" making up the lower level. This might be called "reducing up."

Since there is nothing known about atoms that could cause them to arrange themselves into the shapes of the various known organisms, absolute chance is said to be responsible for variations of form, and the surrounding conditions are said to allow certain ones to persist and multiply.

Once we accept that knowledge is tentative, and that we are probably going to improve our knowledge in important ways when we learn more about the world, we are less likely to reject new information that conflicts with our present ideas. The attitude of expectancy will allow us to apply insights gained at one level of generality to other levels. No particular kind of knowledge will have such authority that it will automatically exclude certain possibilities in another field of knowledge.

For example, either Polanyi's adsorption measurements or the known structures of organisms or biological systems could be seen as an opportunity to ask "what processes could create structures of this sort, or are there rules of stability which can clearly define the conditions under which such a structure can exist?"

Rules of structure-making are likely to be very complex, but rules of stability are relatively simple. Polanyi's adsorption isotherm is a very simple rule of stability, which describes how gas molecules arrange themselves on a surface, and it makes a general contribution to our understanding of the "condensed state of matter. "The factors which govern mammalian fertility can be seen as part of a potential rule of stability, describing the conditions under which new mammals can come into existence; as it turns out, the factors which govern fertility also have an important influence on the subsequent development of the organism, its health, intelligence, and longevity--the way in which its very structure comes into being.

Rules of stability, with greater generality than the basic laws of physics and chemistry, might be discovered which specify the nature of the substance which is likely to exist in various situations. At present, chemical engineers have some fragmentary knowledge of this sort. The attitude of reductionism has certainly kept many things from being discovered, even in chemistry and simple biochemistry. For example, people used to say that, although you can cook a soy bean or a piece of meat into its component amino acids, you could never cook amino acids into a protein. Sidney Fox did just that, simply by omitting the water in the recipe. The reductionists then said that the polymers Fox made would be random, and without any catalytic (enzyme-like) properties, but in fact their structure was non-random, and they did have catalytic activity.

Another example: Some biochemists thought it was foolish to suggest that dilution might obscure important principles of enzyme behavior, when cells are dissolved in water in a test-tube; but a brighter man down the hall thought about it for a while, and demonstrated that some of the most famous soluble test-tube enzymes don't react randomly with molecules in

solution in the cell, but pass the molecule from enzyme to enzyme in an organized way.

In these examples, the ignorant opinions were held by most chemists through most of the history of protein chemistry, because it was required by the reductionist belief that the "parts" explain the whole. The belief that Fox's polymers of amino acids would be "random" and inert derived from the belief that forms are generated randomly, through a long history, and that the properties of life are simply the arbitrary result of what happened to be preserved by the natural selection of the environment.

The existence of various chemical substances in interstellar space, or the presence of "biological" molecules in petroleum, or of subatomic particles in cosmic rays or radioactive minerals, can be understood in terms of various rules of stability. Plant material and human substance might best be understood in terms of such rules of stability. That would put all substances on the same "ontological level," though the more complex substances would have more specialized requirements for existence.

The "requirements for existence," seen in this way, form a direct link between practical matters, such as health and human potentiality, and seemingly remote matters, such as cosmology.

To discover such "rules of stability" for complex structures requires that we imaginatively extend the rules or laws that we now recognize. Such an imaginative extention, in searching for adequate hypotheses, can be seen as an expansion of physics, or as a "reducing up" of physics to biology.

The insistence that formal deductive reasoning should form the link between our present physical ideas, and our

description of biology, is what forces the reductionists to assert that our existence is the result of random mutations plus natural selection. My preference for the use of imagination to extend physical ideas, rather than logical deduction to "apply" those ideas, comes simply from my feeling that we don't yet know everything, and that in searching for new knowledge we should avoid routes that lead us to believe nothing is there even before we have looked.

NOTES:

In directing our attention toward "rules of stability," I think the following are some of the processes and principles we should consider:

Systems in which energy (guiding or driving energy) is added and given off at every point, systems in which no part is in equilibrium. This is how the world is, but it is usually omitted from "scientific" descriptions, because of its complexity.

Asymmetry as a general aspect of interaction.

Hysteresis, or system memory. This is one aspect of the reality of time.

Long range order. This simple idea is often neglected. It is implicit in hysteresis.

Oscillating reactions, as a paradigm for various physical processes, in which energy differences create structure in both space and time.

The processes of resonance as they contribute to stability of structures, and as involved in long-range order, hysteresis, oscillating reactions, asymmetry, etc.

All stability is metastability.

One of my professors, Francis Reithel, pointed out the fundamental importance of Le Chatelier's principle for biochemistry. Another professor, Sidney Bernhard, fundamentally changed and expanded our understanding of biochemistry by showing that glycolytic enzymes operate in a tightly organized system. Human health and the health of the planet are deteriorating in spite of the grandiose claims of the reductionists. Satisfactory solutions to complex problems will be possible only if we directly confront the complexity. Vernadsky concretized Le Chatelier's equilibrium principle in relation to biogeochemistry, and similar methods can probably be applied to many other complex systems. The number of elements and the organizational diversity of elements in the system will have to be taken into account in concretizing and applying the ideas.

CHAPTER 6

THE EX-RAINFORESTS OF THE PACIFIC NORTHWEST

In a recent television piece, Stub Stewart, one of our local timber barons, said that when he looks at an ancient forest he sees money; an average fir tree represents more than $2000, he said. (In Ernst Schachtel's analysis of perception types, this is the lowest, undeveloped or degraded type of perception, based on self-centered utility, rather than on grasping the actual nature of the thing.) Considering that this un-intelligent sort of perception is typical of people who have power, I want to point out some of the neglected money related effects of mature forests of giant trees.

These forests, which the elderly timber baron described as rest homes which should be removed and replaced with kindergartenly tree farms, are often described as being biologically static systems which, for example, make no contribution toward absorbing the carbon dioxide produced by industry. (The people who use this argument would have a point, as far as the carbon dioxide question goes, if they proposed to plant new forests in shopping centers and other places that don't have trees now. But replacing a big forest by a little forest adds carbon dioxide to the environment. I don't consider the "greenhouse effect" to be a problem, but I mention it as an example of how even their own arguments weigh against their intentions.)

The fact that I think is crucial for the world's future is that rainforests energetically are comparable to volcanos,(1)

except that their energy is primarily biological, and that their effects contribute massively to the stability of the biosphere. Although net growth per year (in the sense of added biomass) is greater in a tree farm, the internal flow of energy is greater in an ancient forest than anywhere else on earth, and it is this high rate of "metabolism" which gives the great forests their powerful influence on the rest of the world. Bioenergetically, they can be compared to the brain of an animal: intense, stable, and essential to the existence of the whole.(2,3)

If we imagine an ideal green slime resting on an ideal brown goo (in some future time), we could suppose that the sun's energy was being absorbed and used in photosynthesis with some efficiency at any moment. The difference between this simple system and the rainforest has to do with the complexity of life's interaction with the environment: the great age of the forest reveals the stability of its integration with the world's weather system.

Metabolic processes occurring at night influence daytime processes; winter events influence summer events; soil events influence air events. Time is bound into the system. The flow of energy is dominated by nearly horizontal switchbacks, rather than by uncontrolled vertical surges. Space is bound into the system, for example by the mysteriously powerful pumping systems involved in transpiration. (The secretion of droplets at the ends of leaf-veins under certain conditions shows that osmosis and evaporation are not adequate to explain the movement of water; the attitude of our science establishment to this fundamental problem offers great opportunities for sociological investigation.)

A century ago, Darwin showed that the folding movements of many plants at sunset have the function of preventing radiant heat loss; that is, the leaves arrange themselves so that

they radiate their metabolically derived energy toward other leaves, rather than toward the dark, energy-absorbing sky. He showed that the angle of the leaf at night could make the difference between life and death.

Water is a very good absorber of heat (infrared radiation). For example, a spectrum of the energy radiated from a person's hand reveals a deviation from the expected curve, as a result of infrared absorption by water. The mass of water inside a tree is therefore metabolically relevant, even though most of the metabolism of a tree is near its surface. The height and density of the forest will also affect its thermal and metabolic stability. In humans, about 75% of our metabolic energy is lost as radiant heat. In a cold environment, the energy lost as radiant heat is important to any organism. The radiant interaction of organisms in a rainforest is immense. It is another factor which distinguishes forests from tree farms.

The Food and Agriculture Organization of the U.N. defines forests as "lands bearing vegetative associations dominated by trees of any size, exploited or not, capable of producing wood or of exerting an influence on the local climate or on the water regime." Everyone who listens to weather reports on television and radio should be aware that the forests, and their destruction, are affecting their weather. Farmers and the owners of ski resorts are aware that drouths affect their income, so they shouldn't have too much trouble grasping the implications of deforestation. The loggers talk about the importance of their jobs, relative to the importance of the environment; drouths and floods, caused by deforestation, have obvious economic consequences, which must be taken into account.

Ivory dealers say "but I have to make a living" even if elephants become extinct. Drift-net fishermen say "I have to make a living," even if entire populations of porpoises are

destroyed. Every region and industry seems to have people who feel that their present jobs are more important than the very ecosystem which is the foundation for their present "harvesting" job. This pathological sort of perception resembles the type of autism in which the victim devours part of his own body, unless restrained. Just as Gorbachev said that the survival of humanity transcends the class struggle, protection of the environment must transcend the witless arguments of those who insist that they must be allowed to consume these resources now, before it's too late for them to enjoy this one last harvest.

In Alaska, gigantic Sitka spruce are being turned into wood pulp to make into rayon shirts. In Oregon and Washington, many ancient trees are made into pulp for newsprint and wrapping paper. Redwood is so resistant to decay that houses built from it should last forever, but most of the houses built from the extinct redwood forests have been bulldozed into splinters and hauled to landfills, as the cities grow and change. One California company which had been slowly cutting its large timber holdings was recently forced to begin cutting trees as fast as possible, because of debt created when it was acquired by junk-bond billionaire Hurwitz. The fortunes created by this destruction of wealth are stimulating the concentration of wealth and power, but do not seem to be leading to the production of new wealth. The condition of towns and regions which have depended on the timber industry speaks eloquently of what the timber baron's "wealth" amounts to in human terms.

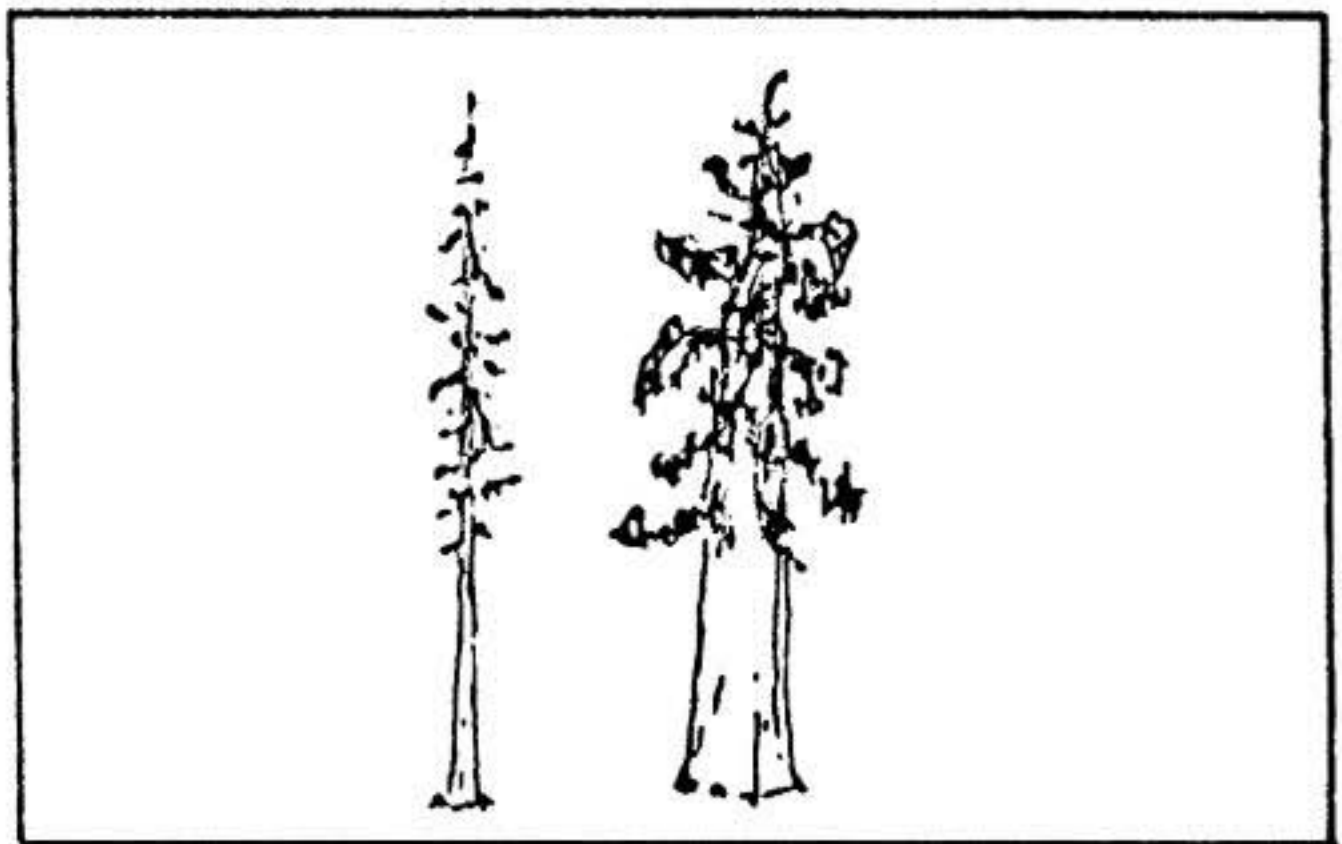
The alternative sources of cellulose for rayon and paper are numerous. Besides cotton, linen, and hemp, various types of paper have been made from straw, esparto grass, jute, sisal, cane, and bamboo. The use of wood for building houses is largely a cultural matter, since there are many better and

cheaper materials. For example, I lived in a two-storey adobe house built around 1450, which had survived several major earthquakes without damage. It had 12 ft. ceilings, and didn't need air conditioning even in hot weather. When the drainage is good, these mud buildings are not damaged even by torrential rains. My father built an adobe house in the 1930's which is still in good condition. Even the shingles were made of clay, mixed with an emulsion of tar for water-proofing. These houses can never be destroyed by fire, and they don't have the toxic fumes often produced by chemically treated wood products.

Even northern forests can provide rich harvests of products other than wood, without causing ecological damage. Resins, drugs, hormones, and food materials are produced in abundance, though the moronic practices of clear-cutting and slash-burning have eliminated some of the potential forest crops. According to the calculations of biologist Curt Mitchell, the forests of Oregon can produce at least $4,000 worth of materials per acre per year other than trees.

About 96% of the redwoods which used to extend from San Francisco to southern Oregon are gone. Only about 2 square miles of redwoods remain in Oregon, and many of these are scheduled to be sold and logged this year. The redwoods illustrate some of the interactions between trees and climate. The coast redwood (Sequoia sempervirens) can reach a height of more than 350 feet. It requires areas which provide summer fog as well as winter rain. In some areas, it is estimated that 50% of the annual precipitation is in the form of fog caught on their leaves, so it is obvious that their great height makes a major contribution to the water-economy of the region.

The Sierra redwood (Sequoiadendron giganteum) grows at a higher elevation, on the western slopes of the Sierra Nevada Mountains of California. Their massive trunks apparently represent an adaptation to the absence of the summer fog--their wood is about 50% water, so the thick trunks function as storage tanks to sustain activity through the dry seasons (Figure 1).



Left, Coastal, right, Sierra Redwood.

Disregarding the soil's water-retaining capacity in an ancient forest, just the storage of water in the trees themselves can amount to thousands of tons per acre; such quantities of water have significance even geologically. According to A.V. Lapo, in *Traces of Bygone Biospheres*, "the content of water in the tissues of living organisms is approximately five times greater than in all the rivers of the globe." "Half the water. . . in the roots of plants is renewed in several minutes. As a result, the water cycle on land is determined almost exclusively by the transpiration of the plants."

The humidity of the air passing through a tree farm is much lower than that passing through a real forest. Locally, this determines what can live and thrive. On a larger scale, differences in temperature and humidity affect wind flow. I think

this is why the humid ocean winds are increasingly being diverted toward British Columbia, and away from Oregon and California, where they used to provide dependable winter precipitation. (Since ocean currents are guided by winds, the disruption of weather patterns is likely to become self-stimulating.)

2500 years ago, Theophrastus recorded cases in which a region's climate was permanently altered by deforestation and swamp draining, with the result that rich agricultural productivity was lost forever. The difference between the small scale of the ancient Greek ecological damage and the present scale of deforestation suggests the scale of the damage which is being done to modern agriculture.

Deforestation of the Pacific Coast is moving from south to north. The areas that are immediately "downwind" from the treeless coast are the places that will feel the earliest effects on their weather. California and Nevada are now facing their fourth consecutive drouth, and have just experienced the driest December in history. Farmers have been warned to expect a 20% cut in water deliveries this summer. The decreased production of food is likely to cost the region several billion dollars this year, and there is no reason to believe that the old weather patterns will return, without the forests.

Since deforestation causes the soil to be washed away, muddy water causes massive destruction of fish. Reservoirs behind dams have filled rapidly with mud, shrinking their storage capacity, and their ability to control floods and to provide water for irrigation.

In the 1920's, an economist, S.G. Strumilin, showed that money spent on education gave a 27-fold return; more recently, J.K. Galbraith said that the return is about 100 times the investment, and is greater than the return on investments in

railroads, dams, or factories. Buckminster Fuller talked about doing more with less; this is the meaning of applying science to economic production maximizing effects while minimizing the means.

To have an economy that develops qualitatively, rather than quantitatively, means that the extractive industries will decrease, while the complexity, intensity and appropriateness of use of the materials will increase steadily. Investment in humanity means increasing productivity and enjoyment, by improving human health, intelligence, skill and knowledge.

While the economists showed the value of investing in traditional schools, the returns would be greater, and the costs smaller, if we began to apply thought and knowledge to understanding the learning process better. The useful part of education is that which stimulates the imagination. The useful part of knowledge is that which expands human possibilities. If the biosphere continues to be degraded, human possibilities will be stunted, at best.

I think we have to start seeing jobs in resource-extraction as an index of poverty, to the extent that they degrade the biosphere. A definition of wealth must consider both quantity and quality of production. Environmentalists and ecologists have to do some intelligent thinking about economics, so they can help the people in power to think more realistically.

The greatest fraud now current in the mass media is the idea that we must choose between the health of our environment and the vitality of the economy or our standard of living. Just as competition from Japan and Germany is causing big corporations to move quickly to get out of the weapons business and to reinvest in the consumer economy, the present anti-environmental direction of our economy depends on relatively few decisions made by big corporations (and supported

by their agents in government). Since they can get away with making stupid decisions, they make them.

The stylish science-talk about global warming doesn't really take very much into account, beyond a few cultural stereotypes. The most important context to take into account is the importance of moving toward an economy which develops qualitatively rather than quantitatively. There is no foreseeable limit to the qualitative development of the economy. If we can shift from an extractive-degradative economy to one which develops by investing in education, science, culture, and human well-being, we will have a future in which to discover whether the biosphere-noosphere has any limits to its developmental potential.

NOTES:

1. In the sense that the heat of volcanos can "drive" changes in ocean currents: winds, "driven" by forests, are the other major influence on the patterns of ocean currents, and thus on the distribution of solar energy around the planet.

2. Following the brain analogy, a system of tree farms is like the anencephalic monster; it can grow if fed, but can never contribute to the world's advance.

3. Rainforests illustrate the first and second principles of biogeochemistry; that biogenic migration of chemical elements tends to the maximum, and that the development of stable life-forms serves this tendency.

PART 2:

ENERGY PROBLEMS

"Energy is the only life, and is from the Body. . . .
Energy is eternal delight."

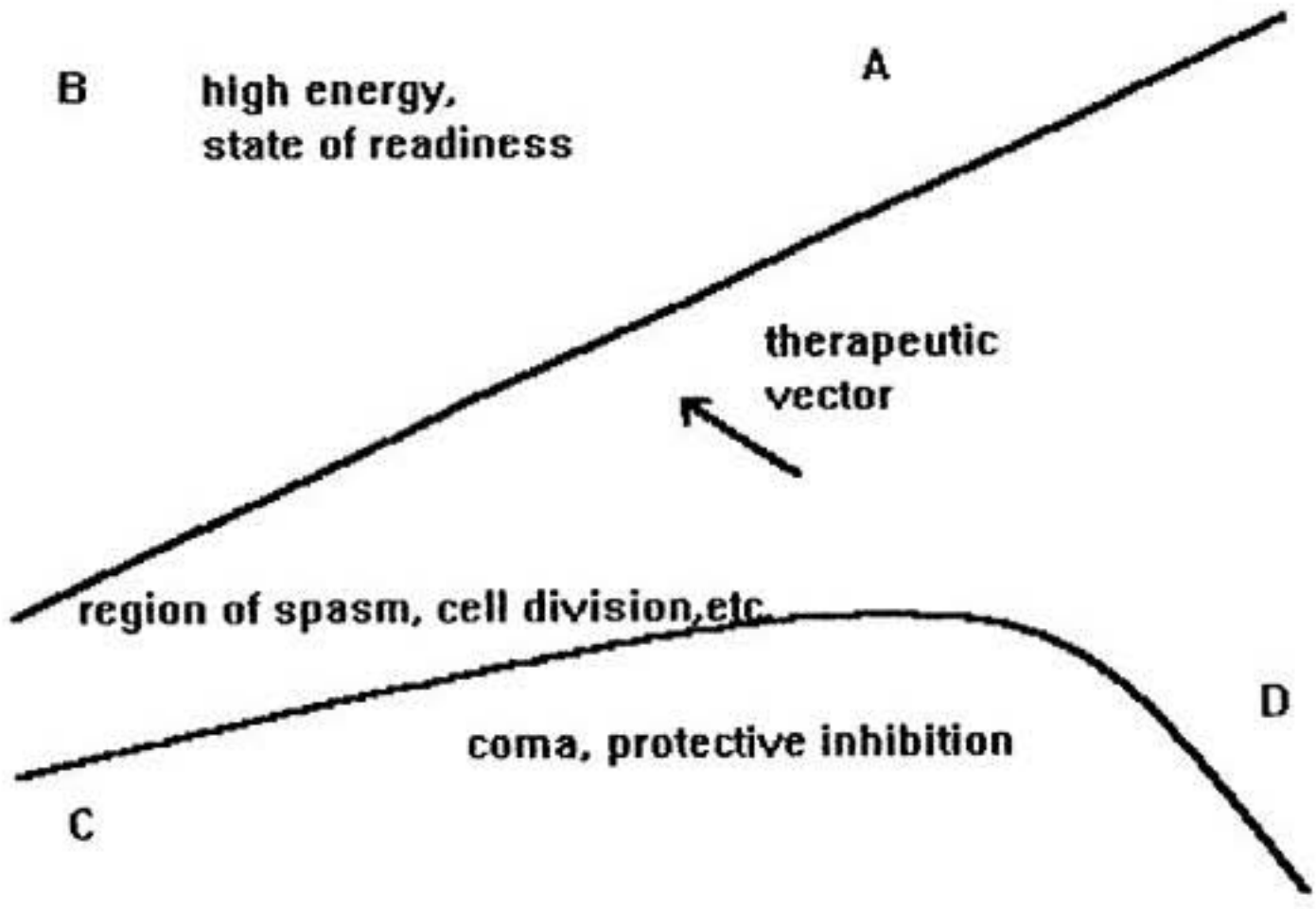
W. Blake

An emphasis on energy is rapidly gaining acceptance in biology, if not in medicine. Just twenty years ago, many biologists denied that Atkinson's idea of the cellular "energy charge" had meaning or relevance for living systems, but the idea is now widely recognized, and most biologists would probably admit that it has at least some relevance for some situations. In this section, I discuss some of the practical consequences and applications of the idea that we should focus on the role of energy in biological adaptation. Energy, in an important sense, is prior to information, especially in the context of biology.

CHAPTER 7

A UNIFYING PRINCIPLE

For many cells, the threshold for excitation (and response) is governed by the energy charge of the cell. This is clearest in the case of brain cells: seizures can be produced by either hypoxia or hypoglycemia, and in the low energy state of hypothyroidism, deep normal sleep is seldom possible. Muscle cells, secretory cells, and immune cells behave similarly. I believe we are at the beginning of a therapeutic revolution based on this, and other closely related principles. It is easiest to understand these relationships if we use a graph, with "energy charge" on one axis, and with "intensity of stimulation" on the other. This graph represents the relationship of an organism to its environment, or of a cell or tissue to its (internal) environment (Figure 1).



The regions labeled with A, B, C, and D can be thought of, for the sake of illustration, as the following functional states of the organism:

A -- Adventure
B -- A baby sleeping
C -- Cautious conserving of energy
D -- Stressed to death.

The ideal therapy is one which restores the cellular energy thoroughly, so the organism regains its full capacity to adapt, and seeks appropriate stimulation. Good nutrition and sleep are sufficient therapy for a healthy young organism. For old or sick organisms, artificial sleep and special nutrition can be useful. The use of sedatives to produce an "artificial coma" is an old technique which is now being used more often to treat drowning victims and other brain-injured patients.

Sedation or anesthesia decreases the use of energy, making it possible to recover a store of energy, and the efficient, relaxed state of readiness that goes with an adequate reserve of energy. Thyroid and other hormones can increase the rate at which energy is produced, but some of the steroid hormones also have the sedative and anesthetic actions which provide the other aspect of recovery: while production of energy increases, wasteful use decreases.

The idea of the "therapeutic vector" means that any treatment should combine preservation of energy with restoration of energy production. Shock, which is a state of suppressed energy production, can be used to illustrate this approach.

Several times in the last 50 years great advances were made in understanding the nature of shock, but they tend to be ignored or forgotten. I think this is because our medical culture

has lacked a unifying principle which would integrate physiology and biochemistry into a functional whole.

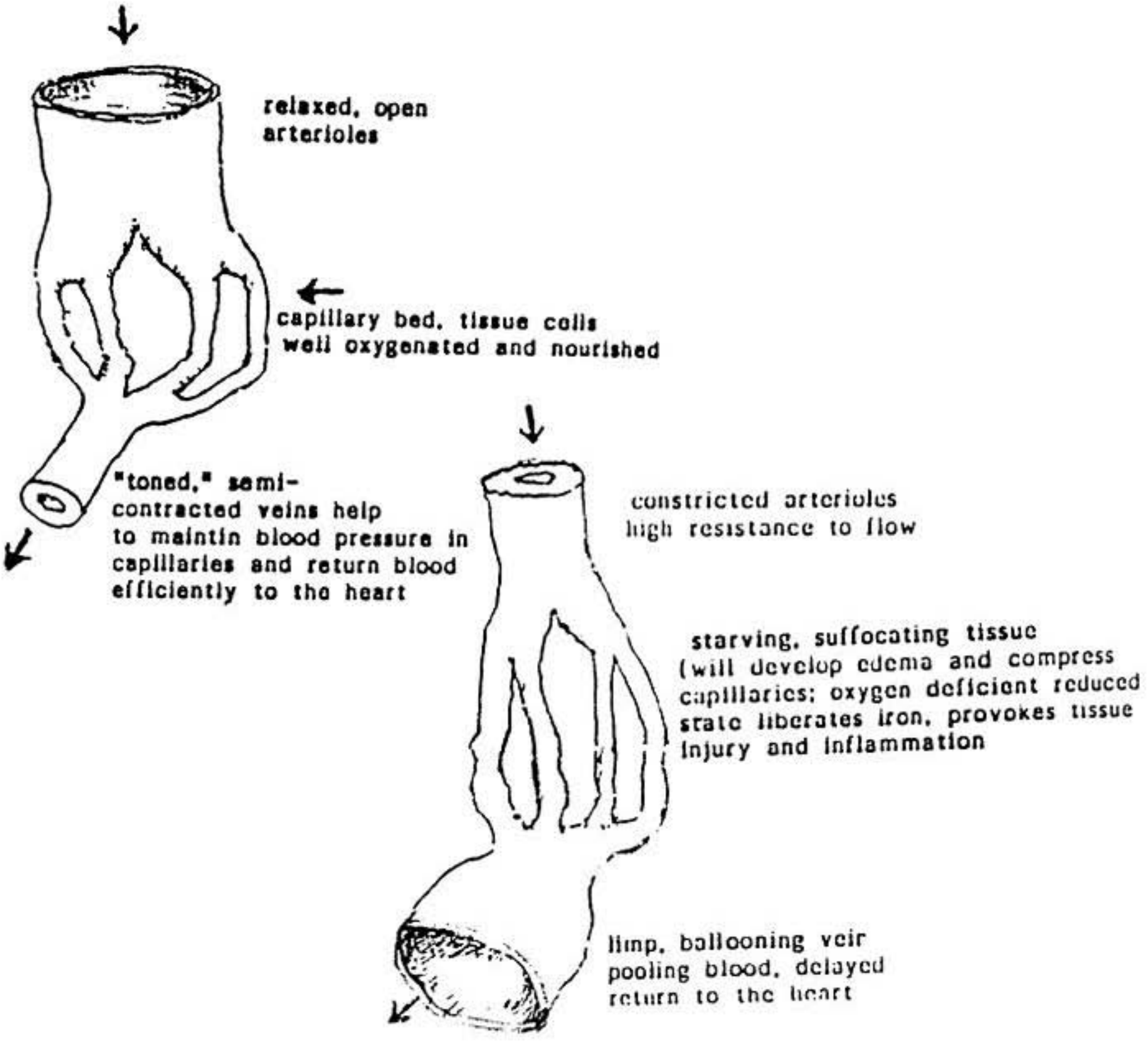
Under extreme conditions, the state of shock can develop. Blood circulation becomes so inefficient that the organism often dies from the shock state itself. It has been traditional to administer adrenalin to shock patients to raise their blood pressure, but adrenalin is often already present at a high level, and more can simply exacerbate the problem. This is because the arterioles contract in shock, and under the influence of adrenalin (and cortisone).

Early in Hans Selye's study of the steroids, he noticed that estrogen treatment causes the same changes which occur in the shock phase of the stress reaction. Many years later I noticed that oxygen deprivation causes the same biochemical changes that occur with an estrogen excess, and with old age, and I proposed that estrogen acts by interfering with the use of oxygen. In the mid-1940s a group of researchers, believing that energy depletion was the basic cause of shock, demonstrated that intravenous injection of the "energy molecule" ATP caused animals to recover which otherwise would have died from shock.

ATP isn't the sort of chemical that is likely to interest the pharmaceutical industry, and although other people have demonstrated that it has therapeutic value in a variety of diseases, the dominant attitude has been to scoff that it is "only a vasodilator." But the tone of smooth muscle in blood vessels is largely a function of the energy charge of the muscle cell. Thus, intravenous glucose can restore the balance between the muscle tone of arteries and veins, and it has been used many times to bring patients out of shock. If a physician is focussing on his patient's extremely low blood pressure, a vasodilator is the last thing he would consider, and salt water is often

preferred in place of glucose, but restoring energy should be the basic aim.

Keeping in mind the relationships between excitation and inhibition discussed above (Figure 1), we can visualize how the energy supply to vascular smooth muscle normally functions as part of a self-regulating system, and how a failure of energy can produce the self-defeating shock state (Figure 2).



In the blood vessels at the left side of Figure 2, the arterioles are in the high energy resting state, while the veins are in the middle, active zone. On the right, the arterioles are receiving "depleted" blood, lacking oxygen or sugar for example, and so are now in the middle energy, active state. Passing through the capillaries, most of the blood's remaining oxygen and nutrients are extracted by the tissue cells, leaving only minimal energy supplies for the veins, which are therefore in the lowest energy state, "protective inhibition," in which there is no muscle tone.

Besides helping to explain the shock state itself, this relationship of vascular tone to cellular energy helps to explain the circulatory distress which is associated with fatigue, old age, hypothyroidism, and estrogen excess.

Bacterial endotoxin causes some of the same effects as adrenalin. When stress reduces circulation to the bowel, causing injury to the barrier function of the intestinal cells, endotoxin can enter the blood, contributing to a shock state, with further impairment of circulation. In old age and in "winter sickness," something like a chronic borderline state of shock can develop. Intravenous glucose has been used successfully to bring patients out of septic shock. The tonic effects of intravenous local anesthetics are, I think, largely the result of their ability to open the arterioles. Magnesium and vitamin A also have some ability to normalize blood vessel tone, and can help to maintain the barrier function of the bowel.

Whether a tissue is hyperactive or underactive, it is possible that a systemic energy deficit is responsible. Symptomatic relief is rational if it is consistent with restoration of energy.

Glucose is often thought of as the most direct source of energy, but other substances are apparently used even more easily. "Ketones" (for example, alpha-keto- or hydroxy-

butyrate) are used more easily, at least in some circumstances. Short and medium chain fatty acids are used more easily than glucose, and it is apparently this fact which accounts for their presence in milk. Their effects on cells--induction of hormone receptors and other specialized cell functions, suppression of stress-induced enzymes, stimulation of energy production in fat cells, inhibition of cancer cell division and viral expression, etc.--are what we would expect of an ideal energy source. Unfortunately, commercial milk animals are fed large amounts of grain, the oils of which act in opposition to the short and medium chain fats. Some tropical fruits and coconut oil provide some of these efficient and protective energy sources. As little as one or two teaspoonfuls of coconut oil per day appears to have a strong protective effect against obesity and cancer.

CHAPTER 8

STEROIDS

This type of molecule might be the most common carbon compound in the universe. It is made by single celled organisms, by plants, and by animals, and has many kinds of function. The steroid hormones are involved in all aspects of animal physiology, and overlap with control functions of the nervous system, peptide hormones, metabolites, prostaglandins, cyclic nucleotides, etc. Sometimes people speak of "steroids" when they mean glucocorticoids such as cortisol or a synthetic like dexamethasone, or, among athletes, when they mean anabolic steroids or synthetic androgens; and so it is common to associate "steroids" with harmful side effects. All foods contain steroids and sterols (a major type, containing an alcohol group and a side-chain) some of which are beneficial and some of which are toxic or allergenic.

In animals, cholesterol is the basic sterol molecule, which is massively converted into other substances, including the steroid hormones. Thyroid hormone and vitamin A are required for this conversion. The first step occurs in the energy-producing mitochondrion, where cholesterol loses its side-chain and is slightly oxidized, producing pregnenolone. Being less fat soluble than cholesterol, pregnenolone leaves the mitochondrion, so it can't inhibit its own synthesis. Rather, it seems to stimulate its own synthesis, though this isn't as clearly established as in the case of progesterone.

Depending on the tissue, pregnenolone will be converted by enzymes in the cytoplasm into either progesterone or DHEA

(dehydroepiandrosterone). The fact that progesterone (and probably pregnenolone) stimulates its own synthesis means that taking it does not suppress the body's ability to synthesize it, as happens with cortisol. Sometimes, one dose or a few doses can restore the body's ability to produce enough of its own.

Progesterone also allows the thyroid gland to secrete its hormones, especially when the thyroid function has been inhibited by estrogen. Since the thyroid hormone is needed to produce progesterone, a supplement of either tends to normalize both thyroid and progesterone production.

Progesterone and DHEA are the precursors for the other more specialized steroid hormones, including cortisol, aldosterone (sodium-retaining hormone), estrogen, and testosterone. The formation of these other hormones is tightly regulated, so that taking the precursor will correct a deficiency of a specialized hormone, but will not create an excess. At least in the case of progesterone, an excess tends to balance or neutralize an excess of the specialized hormone, so it has been described as having anti-androgenic, anti-estrogen, anti-aldosterone, and anti-cortisol functions.

Many steroids have a protective ("catatoxic") action against a wide variety of poisons. Some of the quick effects (e.g., within 10 minutes) of progesterone and pregnenolone probably represent a catatoxic action, as well as a neutralizing or balancing of excessive estrogen or cortisol. Improved metabolic efficiency, sparing oxygen and glucose, will have a quick effect in reducing edema.

During pregnancy, very large amounts of progesterone are made. It protects and stabilizes practically all functions of both the mother and the fetus. Progesterone, glucose and the thyroid hormones powerfully influence the brain development

and intelligence of the baby, probably by influencing both the number and the size of brain cells, and the quality of their functioning.

Part of progesterone's protective effect is a result of its quieting effect on cells. For example, it tends to prevent seizure activity in brain cells. During childbirth, its normal function is to act as an anesthetic. When the level of estrogen is too high, progesterone can't achieve this effect. In a non-pregnant person, it is important to determine the minimum effective dose by taking only a few drops at a time, and repeating this small dose about every 20 minutes until symptoms have been controlled. Otherwise, serious "drunkenness" can be produced, with loss of coordination, and even unconsciousness.

The only solvent for progesterone which isn't toxic and which will dissolve an effective quantity, is vitamin E. In this form, it can be absorbed through the skin or other membranes, or can be taken orally. Taken orally, it is absorbed as chylomicrons, going into the general circulation (as vitamin E does), instead of to the liver where it would be prepared for excretion. In this form, therefore, it is fully and quickly available to all tissues. It is approximately 20 times more powerful in its action than other preparations, so it is important to use it in physiological quantities, rather than in the huge doses commonly given rectally or by injection. Ten or 20 mg. is often an effective dose, though people with low thyroid or high estrogen sometimes use 50 to 100 mg. per day. In the customary 10% solution, one drop contains about 3 mg. progesterone, and 1 ml. (1/4 tsp.) contains 100 mg. The first dose should never be more than 15 mg.

Pregnenolone, taken orally, does nothing noticeable to a healthy animal or person, but if the stress-related hormones

are elevated, they return to normal when pregnenolone is taken. The brain contains much more pregnenolone, DHEA, and progesterone than do other organs or the blood, and these levels decrease progressively with age. Older people are more likely to feel an effect from pregnenolone, than are young people. A tenth of a gram is a reasonable first dose, though some people seem to need as much as 1 gram per day.

CHAPTER 9

THYROID

Measuring the amount of thyroid hormone in the blood isn't a good way to evaluate adequacy of thyroid function, since the response of tissues to the hormone can be suppressed (for example, by unsaturated fats).

In the 1930's accurate diagnosis was made by evaluating a variety of indications, including basal oxygen consumption, serum cholesterol level, pulse rate, temperature, carotenemia, bowel function, and quality of hair and skin. A good estimate can be made using only the temperature and pulse rate.

Oral or armpit temperature, in the morning before getting out of bed, should be around 98° F, and it should rise to 98.6° by mid-morning. This is not valid if you sleep under an electric blanket, or if the weather is hot and humid. A person who is hypothyroid produces heat at a low rate, but doesn't lose it at the normal rate, since there is less sweating, and the skin is relatively cool. Many hypothyroid people compensate with high adrenalin production (sometimes 40 times higher than normal), and this tends to keep the skin cool, especially on the hands, feet, and nose. The high adrenalin is the consequence of low blood glucose, so a feeding of carbohydrate, such as a glass of orange juice, will sometimes lower the pulse rate momentarily. Healthy populations have an average resting pulse rate of about 85 per minute. Especially in hot weather it is useful to consider both temperature and pulse rate.

The Achilles tendon reflex is another quick way to estimate thyroid function. This reflex is used because of the

insignificant weight of the toes in relation to contraction of the gastrocnemius muscle. The T (repolarization) wave on the electrocardiogram is a similar indicator of the rate of energy production. Thumping the Achilles tendon causes the muscle to contract (unless it is already in a semi-contracted state, which isn't uncommon). The contraction consumes energy, and the muscle can't relax until enough energy has been produced to restore the threshold and the readiness for a new contraction.

If energy production is efficient, relaxation is faster than the passive return motion of the foot, so the foot swings freely back to its original position, and over-shoots slightly, causing a slight swinging action. In hypothyroidism, the foot returns as if controlled by a pneumatic door-closer, and settles slowly and precisely into its relaxed position, sometimes with a hesitating, intermittent motion. This slow replenishment of energy, and slow relaxation, can cause muscles to cramp easily. The aching leg muscles of children at the end of an active day are often a sign of hypothyroidism, and sometimes the gastrocnemius muscle becomes very swollen and hypertrophied in hypothyroid children. The same process, of slow energy regeneration, can cause rhythm disturbance in the heart, and often causes insomnia and restless sleep.

The thyroid gland secretes about 3 parts of thyroxin to one part of triiodothyronine, and this allows the liver to regulate thyroid function, by converting more of the T_4 to the active T_3 when there is an abundance of energy. Glucose is essential for the conversion, so during fasting there is a sharp decrease in metabolic rate, and in experiments, 200 or 300 calories of carbohydrates can be added to the diet without causing fat storage.

When the liver is the main cause of hypothyroidism, your temperature (and especially the temperature of your nose, hands and feet) will fall when you are hungry, and will rise when you eat carbohydrates. If a hypothyroid person has a very slow pulse, and feels lethargic, it seems that there is little adrenalin; in this case, a feeding of carbohydrate is likely to increase both the pulse rate and the temperature, as the liver is permitted to form the active T_3 hormone.

Women often have above-average thyroxin, with symptoms of hypothyroidism. This is apparently because it isn't being converted to the active form (T_3). Before using a Cytomel (T_3) supplement, it might be possible to solve the problem with diet alone. A piece of fruit or a glass of juice or milk between meals, and adequate animal protein (or potato protein) in the diet is sometimes enough to allow the liver to produce the hormone. If Cytomel is used, it is efficient to approximate the physiological rate of T_3 formation, by nibbling one (10 or 25 mcg.) tablet during the day. When a large amount is taken at one time, the liver is likely to convert much of it to the inactive reverse-T_3 form, in a normal defensive response.

Women normally have less active livers than men do. Estrogen can have a directly toxic effect on the liver, but the normal reason for the difference is probably that temperature and thyroid function strongly influence the liver, and are generally lower in women than in men. Estrogen inhibits the secretion of hormone by the thyroid gland itself, probably by inhibiting the proteolytic enzyme which dissolves the colloid. Progesterone has the opposite effect, promoting the release of the hormones from the gland. At puberty, in pregnancy, and at menopause, the thyroid gland often enlarges, probably as a result of estrogen dominance.

Thyroid function stimulates the liver to inactivate estrogen for excretion, so estrogen dominance can create a vicious circle, in which excess estrogen (or deficient progesterone) blocks thyroid secretion, causing the liver to allow estrogen to accumulate to even higher levels. Progesterone (even one dose, in some cases) can break the cycle. However, if the gland is very big, the person can experience a few months of hyperthyroidism, as the gland returns to normal. It is better to allow the enlarged gland to shrink more slowly by using a thyroid supplement. If an enlarged gland does begin to secrete too much thyroid hormone, it can be controlled with tablets of propylthiouracil, or even with raw cabbage or cabbage juice, and cysteine-rich meats, including liver.

Besides fasting, or chronic protein deficiency, the common causes of hypothyroidism are excessive stress or "aerobic" (i.e., anaerobic) exercise, and diets containing beans, lentils, nuts, unsaturated fats (including carotene), and undercooked broccoli, cauliflower, cabbage, or mustard greens. Many health conscious people become hypothyroid with a synergistic program of undercooked vegetables, legumes instead of animal proteins, oils instead of butter, carotene instead of vitamin A, and breathless exercise instead of a stimulating life.

CHAPTER 10

THE STRESS OF DARKNESS

Cortisol begins to rise as soon as there is darkness, regardless of sleep or waking. Artificial light, and its absence, clearly can determine the time at which cortisol begins to rise.

Falling glucose is the signal for cortisol to rise. Dreams are closely associated with the chemical-physiological mobilization in response to low blood glucose. (Rising adrenalin probably mediates the cortisol response to decreasing glucose.)

Sleep minimizes the increase of cortisol. The inhibitory, sleep inducing brain chemicals, GABA and the sleep peptide, have a quieting, anti-stress effect even during waking stress.[1] Sleep (and the inhibitory chemicals) reduce energy expenditures, conserving glucose.

The mitochondria, by their ability to use oxygen, are responsible for the normal efficient use of glucose.

Beginning at sunset, darkness progressively damages mitochondria structurally and functionally. Mitochondrial damage, and the functional impairment of organs such as the heart muscle, reach a peak at dawn.[2]

During the day (in organisms which survive the night), mitochondrial structure is restored, and organ function improves, with the peak being reached at sunset.

In winter, there is cumulative damage to mitochondria, because of too few daylight hours to complete the rebuilding of

mitochondria.[3] During the summer (in organisms that live long enough) the cumulative damage is mostly repaired.

A residue of altered cell and tissue structure, and of impaired enzyme function, remains under natural conditions of day-night cycles.

In the dark of polar winter, ordinary artificial light provides some protection during the 16 hours when it is used, but during the dark hours when lights are off, healthy young people show the darkness-related signs that normally occur in older people, such as an accelerated pulse.[4]

Although direct sunlight damages skin, people generally are healthier in proportion to their exposure to sunlight.

Ultraviolet and blue light produce free radicals in living material, but they penetrate only a few millimeters into tissue. Yellow, orange, red, and infrared rays penetrate much more deeply.

Small organisms are able to set their biorhythms by a very weak light. Only bright lights can alter human rhythms. For example, the cycle of body temperature can be changed, or the rhythmic secretion of melatonin can be suppressed by lights stronger than 2500 lux.[5]

Three common biological pigments are able to absorb the penetrating red light: Biliverdin, blue copper proteins, and melanin.

The presence of melanin in nerves suggests that it should be considered as a candidate for the pigment which allows light entrainment of rhythmic melatonin secretion.

The presence of copper proteins in every cell, and in the mitochondria, suggests that they should be candidates for the

red light receptor which promotes respiratory function and restoration of the mitochondria.

The presence of copper in the crucial respiratory enzyme, cytochrome oxidase, is of the greatest interest.

Both copper and light appear to be involved in other aspects of respiration, including cyanide detoxification,[6] and possibly even in activation of the thyroid hormone.[7]

Besides darkness, hypoxia and overload stress (which is relative hypoxia, in a sense) are the main things which damage mitochondria. Inhibitory analogs of GABA appear to be protective in all types of stress. The anesthetic steroids, such as progesterone, pregnenolone (and possibly DHEA), also protect against injury by stress, and probably work by some of the same energy-sparing mechanisms.

Anti-dark-stress substances would tend to minimize nocturnal hypoglycemia by various mechanisms, including the inhibition of insulin secretion. Acetylcholine and estrogen stimulate insulin secretion, so cholinolytics (e.g., atropine) and antiestrogens (e.g., progesterone and DHEA) would tend to inhibit it, and GABA helps by causing insulin uptake by red blood cells.[8]

Both living at a high elevation and having high thyroid function increase the quantity of mitochondria in cells, and this increase appears to be fairly permanent. Pretreatment with thyroid hormone or with a time at high altitude increases the ability to resist stress.

Living at high elevation or having high thyroid function also increases the vascularity of tissues, that is, the number of capillaries per unit of tissue, and increases the quantity of blood in the tissue, protecting against hypoxia.

Avoiding excessive intake of unsaturated fatty acids and iron will decrease the damage caused by unavoidable stress (including darkness).

Analogs of the inhibitory nerve transmitter, GABA, protect against damage to the mitochondria in the natural way that sleep does, minimizing the injury caused by cortisol. Milk and various fruits contain close analogs of GABA, some of which specifically block formation of the catabolic stress enzymes.

To the extent that nocturnal stress resembles shock, taking some extra salt at bed-time is logical. It lowers adrenalin, and tends to increase blood volume. In hypoxic stress, tissue retains water, and increasing the sodium content of the blood opposes that tendency. It is often a remedy for insomnia.

Penetrating red light is possibly the fundamental anti-stress factor for all organisms. The chronic deficiency of such light is, I think, the best explanation for the deterioration which occurs with aging. Enzyme changes, free radical changes, structural and respiratory changes are all involved as consequences of darkness stress.

Just as there are multiple hormonal and nervous systems which ensure the reliability of our physiology, we should expect red light to have more than one beneficial function. For example, it could quench excited electrons, desorb inhibitory toxins, maintain enzyme function, mobilize stored copper, and regulate the conductivity of subcellular structures. Red light, applied within the first several minutes following x-ray or gamma irradiation, protects organisms (from bacteria to mammals) from radiation injury.[9] The activation of energy-dependent repair processes is clearly involved, but the exact physical and chemical mechanisms still haven't been determined.

During the winter when there isn't enough sunlight, it is helpful to use several hundred watts of incandescent lights. If bulbs with internal reflectors are used, 500 or 600 watts can be bright enough to have a protective biological effect.

NOTES

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CHAPTER 11

PREGNENOLONE

My interest in pregnenolone was the result of an accident. I had been experimenting with the solubility of various steroids. I found that pregnenolone isn't very soluble in vitamin E, and I saved the bottle containing vitamin E and pregnenolone to use as a vitamin E supplement. I had another bottle of pure vitamin E.

In 1983, the ocean current called El Nino caused Oregon's weather to stay cloudy and rainy through the summer. I didn't have my usual summer recovery from "winter sickness," and by November I was becoming very sick. During a two week trip I felt perfectly well, but except for that short time I kept getting sicker and sicker (with inflammation of arteries, dental abscesses, asthma, migraines, and colitis). Lying in bed one day trying to understand what had happened during that two-week trip, I remembered that I had used the vitamin E containing a residue of pregnenolone on the trip, but used pure vitamin E after I got home. I immediately got out of bed and took a pinch of pregnenolone. In about an hour, all of my symptoms had stopped, and for over a week I was healthy and energetic. But then I got sick again, and was so distracted by the pain that it was several days before I remembered the pregnenolone. Another pinch had the same dramatic sudden effect. Since then I have taken some almost every day. While I was sick I had pictures made for a passport, but they looked so odd that I got several more. The best of those, the least haggard looking, is reproduced here.

BEFORE PREGNENOLONE: Years of declining health with "winter sickness." Photograph July, 1983. Note the drooping skin. Eyelids were covered by the sagging skin.

AFTER PREGNENOLONE: About ten weeks using 50 to 100 mg. per day. Photograph mid-September, 1984. I suspect that connective tissue cells contract almost like smooth muscle under the effects of pregnenolone; there seems to be turgor without edema.

Pregnenolone is known to be produced (in the mitochondria) from cholesterol. This is the first stage in the production of all of the steroid hormones. If pregnenolone synthesis is insufficient, supplementary pregnenolone would help to maintain an optimum level of the various other steroids. Aging, stress, depression, hypothyroidism, and exposure to toxins are conditions in which synthesis of pregnenolone might be inadequate.

In 1944 factory workers were given daily doses of pregnenolone and, on alternate weeks, a placebo. During the pregnenolone weeks, their piece-work output was significantly higher. Healthy young people who are not under stress do not feel anything from taking even a very large dose (e.g., one gram), and no changes have been detected in blood glucose, proteins, amino acids, or salts. The urine apparently contains more conjugated steroids (indicated by an increased tendency to foam) after taking a large dose of pregnenolone; I think light is the main factor normally causing changes in the conjugated steroid content of urine.

The skin and the brain are important sites of steroid synthesis, and they are usually ignored by endocrinologists investigating steroid hormones. Papa and Kligman (1965) showed that adding pregnenolone or progesterone topically to skin would restore youthful properties to aged skin. I think DHEA gives similar results, and (like progesterone) is more easily absorbed than pregnenolone. Both progesterone and pregnenolone seem to improve the efficiency of blood circulation. I have seen grey-skinned depressed people turn pink and start smiling shortly after taking pregnenolone.

About 1950, pregnenolone was tested on several people with exophthalmia from Graves' disease, and it was reported that their eyes quickly receded toward a more normal position in their sockets. Having read this, I mentioned it to a desperate woman with horribly bulging eyes. Her left eyeball was about 50% exposed, and the other one was less extreme, but still seriously protuberant. She took some pregnenolone as we talked, and within an hour it seemed to me that her eyes were receding. An hour after she took the pregnenolone, she said her eyes were feeling much better. I left her city early the next morning, but she telephoned me the next day and claimed that her eyes were completely normal. Without seeing her, I

don't know exactly what she meant by "normal." This happened over two years ago, and I hope to visit her city soon to see whether her eyes really became, and stayed, normal.

For many years it has been known that steroids, including cholesterol, have an anti-toxic effect. The cytochrome P-450 family of enzymes are an important factor in our resistance to toxins. Moderate amounts of cortisol promote this system, but larger amounts degrade it. Pregnenolone doesn't affect the rate of synthesis of these enzymes, but it stabilizes them against the normal proteolytic enzymes, increasing their activity. I believe this stabilizing action is a general feature of these steroids, explaining other anti-toxic effects such as blocking hemolysis, and probably many features of growth and differentiation, including control of cell division and prevention of atrophy.

NOTE:

After using pregnenolone for several years, I noticed that the slack skin and other signs of aging were coming back. That spring I increased my dose of pregnenolone, and did other things to promote my own pregnenolone synthesis, such as using larger amounts of coconut oil and getting a little more exposure to incandescent light. The effects of the supplements are more noticeable in the summer, since that is when the body's repair processes are greatest. Avoiding the destructive effects of northern winters (without migrating to the south) would seem to require artificial lights as bright as summer daylight.

CHAPTER 12

RESTORING HAIR COLOR

Largely because of Albert Szent-Gyorgyi's explorations in biological pigments as factors in cell-regulation and immunity, I have paid special attention to several pigments, such as melanin, the black or brown pigment of hair and skin, of injured potatoes, and of certain fungi, when damaged. When I lived in Montana, I knew many people whose hair became grey in their late 20s; I wondered whether it was caused by low thyroid, by an odd mineral balance, by frequent chilling of the skin and scalp, or maybe just by their lack of fresh fruit and vegetables. In Mexico, people in warm, humid tropical areas seldom lost their pigment. When I heard Carl Pfeiffer speak, I noticed that both his skin and his hair were free of pigment, though he was not an albino, and I wondered whether his various mineral nutritional supplements had contributed to his fading. (He took sulfur every day, and avoided copper. He also advocated the use of molybdenum as a nutritional supplement.)

Until I was 4 or 5, my hair was white, and I took it as a humiliating stigma of sexual immaturity; in fact, everyone tends to darken as they grow up, especially around puberty. Many people have wondered what function the melanin in frogs' eggs might have, and a few years ago someone demonstrated that it is what binds progesterone in the egg, and suggested that it might have a similar function in other animals and other cells.

A Japanese researcher found that each hair color is associated with a certain pattern of several trace minerals. When he removed all the trace minerals, every type of hair became white. When he added a characteristic pattern of trace minerals, associated with a particular hair color, to a sample of demineralized hair, the color which was produced corresponded to the minerals added, and not to what the original color of the hair had been. He concluded that people inherit a tendency to concentrate certain minerals in their hair.

People who studied the effects of steroids on aging skin found that the steroids which reversed structural age changes in the skin (progesterone, testosterone, pregnenolone) sometimes restored hair growth. Occasionally, the hair that grew was pigmented. Estrogen and cortisone accelerated the structural changes of aging in the skin, but their effects on hair were not mentioned. Vitamin A has anti-estrogen effects in skin and other tissues, and part of this effect might result from its ability to promote synthesis of pregnenolone and progesterone.

Physicians have mentioned that a depigmented spot sometimes appears in the skin over an area where they have injected cortisone. The familiar association of severe stress with sudden greying of the hair also would suggest that excessive cortisone destroys melanin. The average stress caused by a particular climate would probably combine with any other factors that are involved in regions where there is more or less white hair than average.

I think oxygen wastage is a central event in aging. Just as a cut potato requires oxygen to make melanin, so do our tissues. Iron tends to keep accumulating in our tissues with aging, and iron appears to be a factor in wasting oxygen (especially in age pigment). When oxygen is deficient, iron

becomes very toxic. Copper is involved in a process which restores iron to its non-toxic form.

Vitamin C in excess can contribute to the toxicity of iron, but in the right amount, vitamin C is metabolically linked with vitamin E in protecting against the toxic free radicals produced by iron. Vitamin A also functions as an anti-oxidant, when the amount of oxygen present is very low--which is when iron toxicity is at its worst.

Someone suspected that copper accelerated aging by causing free radical reactions, and fed a chelator (gluconic acid) to animals, and extended their lives by 10 or 12%. In his next experiment, he fed them both the chelator and extra copper, thinking he would counteract the life extension, but these animals lived 22% longer. He next fed copper alone, and found that it extended the life-span by about 11%, so its effect was additive with that of the chelator. I suspect the chelator was removing iron, and maybe other toxic metals. At a dose about 50 times larger than normal, copper did shorten the life-span by several percent.

Black sheep will produce white wool if they are fed an excess of molybdenum. This is supposedly caused by a displacement of copper. I think we probably accumulate too much of the wrong metals, such as iron, with aging and stress.

I had some eyebrow hairs that were pure white; when one matured and fell out, another white one would replace it. They grow quickly, and have a short life cycle, so they are nice to experiment with.

I went on a very low iron diet, eating mostly milk, with some eggs, cheese, and citrus fruit, but with very little meat for several weeks. I cooked eggs in a copper pan, to increase my copper intake and to avoid iron absorbed from an iron

pan. I found a source of vitamin A without preservative, and began using large amounts of that, which I had not done for several years because of an allergy to the preservative. I increased my doses of DHEA and pregnenolone.

Usually on alternate days, I would rub vitamin A and vitamin E (sometimes with DHEA), or a solution of copper acetate, into the skin around the white hairs. Within a few weeks, the bottom of one of the white hairs had begun to darken (Figure 1--the hair on the right). Another hair (the center one) came out a couple of weeks later, and was darkened along about half of its length. The third hair (on the left) came out two or three weeks later, and was all black except for 3 millimeters at the tip, which had begun growing about the time the other two were changing color. It has been about two months since I stopped cooking regularly in copper (the taste gets very tiresome), and none of the hairs has reverted to white. (The black lines were about 2 mm. apart; they allow both colors to be seen in the xerox copy.) The fine tops of the hairs end at lines 8, 9, and 7, going from left to right; each hair has a few mm. of intermediate light brown, which doesn't reproduce well.

Fig. 1 – Eyebrow hairs darkening from the root up.

CHAPTER 13

ARTHRITIS AND HORMONE BALANCING

A very healthy 71 year-old man was under his house repairing the foundation, when a support slipped and let the house fall far enough to break some facial bones. During his recovery, he developed arthritis in his hands. It is fairly common for arthritis to appear shortly after an accident, a shock, or surgery, and Hans Selye's famous work with rats shows that when stress exhausts the adrenal glands (so they are unable to produce normal amounts of cortisone and related steroid hormones), arthritis and other "degenerative" diseases are likely to develop.

But when this man went to his doctor to "get something for his arthritis," he was annoyed that the doctor insisted on giving him a complete physical exam, and wouldn't give him a shot of cortisone. The examination showed low thyroid function, and the doctor prescribed a supplement of thyroid extract, explaining that arthritis is one of the many symptoms of hypothyroidism. The patient agreed to take the thyroid, but for several days he grumbled about the doctor "fixing something that wasn't wrong" with him, and ignoring his arthritis. But in less than two weeks, the arthritis had entirely disappeared. He lived to be 89, without a recurrence of arthritis. (He died iatrogenically, while in good health.)

Selye's work with the diseases of stress, and the anti-stress hormones of the adrenal cortex, helped many scientists to think more clearly about the interaction of the organism with its environment, but it has led others to focus too narrowly on

hormones of the adrenal cortex (such as cortisol and cortisone), and to forget the older knowledge about natural resistance. There are probably only a few physicians now practicing who would remember to check for hypothyroidism in an arthritis patient, or in other stress-related conditions. Hypothyroidism is a common cause of adrenal insufficiency, but it also has some direct effects on joint tissues. In chronic hypothyroidism (myxedema and cretinism), knees and elbows are often bent abnormally.

By the 1930's, it was well established that the resistance of the organism depended on the energy produced by respiration under the influence of the thyroid gland, as well as on the adrenal hormones, and that the hormones of pregnancy (especially progesterone) could substitute for the adrenal hormones. In a sense, the thyroid hormone is the basic anti-stress hormone, since it is required for the production of the adrenal and pregnancy hormones.

A contemporary researcher, F. Z. Meerson, is putting together a picture of the biological processes involved in adapting to stress, including energy production, nutrition, hormones, and changes in cell structure.

While one of Selye's earliest observations related gastrointestinal bleeding to stress, Meerson's work has revealed in a detailed way how the usually beneficial hormone of adaptation, cortisone, can cause so many other harmful effects when its action is too prolonged or too intense.

Some of the harmful effects of the cortisone class of drugs (other than gastro-intestinal bleeding) are: Hypertension, osteoporosis, delayed healing, atrophy of the skin, convulsions, cataracts, glaucoma, protruding eyes, psychic derangements, menstrual irregularities, and loss of immunity allowing infections (or cancer) to spread.

While normal thyroid function is required for the secretion of the adrenal hormones, the basic signal which causes cortisone to be formed is a drop in the blood glucose level. The increased energy requirement of any stress tends to cause the blood sugar to fall slightly, but hypothyroidism itself tends to depress blood sugar.

The person with low thyroid function is more likely than a normal person to require cortisone to cope with a certain amount of stress. However, if large amounts of cortisone are produced for a long time, the toxic effects of the hormone begin to appear. According to Meerson, heart attacks are provoked and aggravated by the cortisone produced during stress. (Meerson and his colleagues have demonstrated that the progress of a heart attack can be halted by a treatment including natural substances such as vitamin E and magnesium.)

While hypothyroidism makes the body require more cortisone to sustain blood sugar and energy production, it also limits the ability to produce cortisone, so in some cases stress produces symptoms resulting from a deficiency of cortisone, including various forms of arthritis and more generalized types of chronic inflammation.

Often, a small physiological dose of natural hydrocortisone can help the patient meet the stress, without causing harmful side-effects. While treating the symptoms with cortisone for a short time, it is important to try to learn the basic cause of the problem, by checking for hypothyroidism, vitamin A deficiency, protein deficiency, a lack of sunlight, etc. (I suspect that light on the skin directly increases the skin's production of steroids, without depending on other organs. Different steroids probably involve different frequencies of light, but orange and red light seem to be important frequencies.) Using cortisone

in this way, physiologically rather than pharmacologically, it is not likely to cause the serious problems mentioned above.

Stress-induced cortisone deficiency is thought to be a factor in a great variety of unpleasant conditions, from allergies to ulcerative colitis, and in many forms of arthritis. The stress which can cause a cortisone deficiency is even more likely to disturb formation of progesterone and thyroid hormone, so the fact that cortisone can relieve symptoms does not mean that it has corrected the problem.

According to the *Physicians' Desk Reference*, hormones similar to cortisone are useful for treating rheumatoid arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, acute gouty arthritis, acute nonspecific tenosynovitis, psoriatic arthritis, ankylosing spondylitis, acute and subacute bursitis, and epicondylitis.

Although cortisone supplementation can help in a great variety of stress-related diseases, no cure will take place unless the basic cause is discovered. Besides the thyroid, the other class of adaptive hormones which are often out of balance in the diseases of stress, is the group of hormones produced mainly by the gonads: the "reproductive hormones." During pregnancy these hormones serve to protect the developing baby from the stresses suffered by the mother, but the same hormones function as part to the protective anti-stress system in the non-pregnant individual, though at a lower level.

Some forms of arthritis are known to improve or even to disappear during pregnancy. As mentioned above, the hormones of pregnancy can make up for a lack of adrenal cortex hormones. During a healthy pregnancy, many hormones are present in increased amounts, including the thyroid hormones. Progesterone, which is the most abundant hormone of

pregnancy, has both anti-inflammatory and anesthetic actions, which would be of obvious benefit in arthritis.

There are other protective hormones which are increased during pregnancy. These include DHEA, which is being studied for its anti-aging, anti-cancer, and anti-obesity effects. (One of the reasons that is frequently given for the fact that this hormone hasn't been studied more widely is that, as a natural substance, it has not been monopolized by a drug patent, and so no drug company has been willing to invest money in studying its medical uses.) Some of these hormones also have the ability to control cell division, which would be important in forms of arthritis that involve invasive tissue growth. Since DHEA can be easily metabolized into testosterone (by the skin, for example), and into estrogen, I don't think it should ever be administered alone, without an approximately natural balance of pregnenolone and progesterone.

While these substances, so abundant in pregnancy, have the ability to substitute for cortisone, they can also be used by the adrenal glands to produce cortisol and related hormones. But probably the most surprising property of these natural steroids is that they protect against the toxic side-effects of excessive adrenal hormones. And they seem to have no side-effects of their own; after about fifty years of medical use, no toxic side effects have been found for progesterone or pregnenolone.

Pregnenolone is the material the body uses to form either progesterone or DHEA. Other natural hormones, including DHEA, haven't been studied for so long, but the high levels which are normally present in healthy people would suggest that replacement doses, to restore those normal levels, would not be likely to produce toxic side effects. And, considering the terrible side effects of the drugs that are now widely used,

these drugs would be justifiable simply to prevent some of the toxic effects of conventional treatment. Especially during pregnancy, it would seem logical to use the natural hormones and to avoid toxic drugs.

It takes a new way of thinking to understand that these protective substances protect against an excess of the adrenal steroids, as well as making up for a deficiency. Several of these natural hormones also have a protective action against various poisons--Selye called this their "catatoxic" effect.

Besides many people whose arthritis improved with only thyroid supplementation, I have seen more than 30 people use one or more of these other natural hormones for various types of arthritis, usually with a topical application. Often the pain is relieved within a few minutes. I know of several other people who used progesterone topically for inflamed tendons, damaged cartilage, or other inflammations. Only one of these, a woman with rheumatoid arthritis in many joints, had no significant improvement. An hour after she had applied it to her hands and feet, she enthusiastically reported that her ankle had stopped hurting, but after this she said she had no noticeable improvement. (I applied it the first time, but I never saw her again, and I suspect she didn't apply it as thoroughly as I had, mixing it with oil at the time of application.)

We often hear that "there is no cure for arthritis, because the causes are not known." If the cause is an imbalance in the normal hormones of adaptation and resistance, then eliminating the cause by restoring balance will produce a true cure.

But if it is more profitable to sell powerful drugs than to sell the nutrients needed to form natural hormones (or to supplement those natural hormones) we can't expect the drug companies to spend any money investigating that sort of cure. And at present the arthritis market amounts to billions of

dollars in drug sales each year. A drug company representative recently told me that a substance which cures arthritis isn't a desirable product; a good drug (from his company's point of view) is one that has to be used for the rest of the patient's life.

CHAPTER 14

THE CARPAL TUNNEL SYNDROME

When a physician chooses the most profitable diagnostic and therapeutic approaches to a health problem, it is likely to be considered fraudulent if the doctor is a chiropractor, but not if the doctor is a surgeon. If a naturopath tells you that bed rest is the best treatment for a ruptured spinal disc, surgeons will warn you about the dangers of quackery, but the research clearly shows that, for safety and efficacy, surgery is distinctly inferior to bed rest.

There are many other situations in which doing nothing, or using a more conservative treatment, is clearly superior to the standard medical or surgical treatment, but the medical industry has learned how to control public opinion by manipulating the mass media.

By consulting with thousands of women who believed they had a hormone imbalance of some sort that their physicians couldn't identify, I began to see several clusters of symptoms that responded immediately to a rational nutritional and hormonal anti-stress program. One of these clusters might be called Subtle Constellation of Absorbed-Mucoprotein-related signs and symptoms, or possibly sub-clinical myxedema, though neither term is likely to be widely adopted in the medical community.

Women are several times more likely than men to have "thyroid disease," simply because estrogen tends to block thyroid function. Estrogen-induced thyroid hypo-function can be compensated to some degree by various hormonal

adjustments; elevated secretion of adrenalin and cortisol are common. When the compensation is inadequate, there will often be hypoglycemia and a tendency to form too much histamine. Too much adrenalin will cause cold hands and feet, too little will cause orthostatic hypotension (blacking out when you stand up too quickly) and bowel spasms, for example.

Various water-binding glycoproteins are formed under the influence of hormones or stress, but whatever proteins are in the blood, including albumin, will show up outside the blood vessels, around the tissue cells, when the blood vessels become leaky. Low thyroid, high estrogen, and high histamine are known to increase the permeability of blood vessels.

Patients who have myxedema typically have mitral valve prolapse, and at autopsy it can be seen that the valve is thickened into a jelly-like mass. Many women with the premenstrual syndrome have a mitral valve heart murmur premenstrually, but not at other times of the month. The jelly can be formed and removed fairly quickly.

Old text-books on the thyroid gland often listed emphysema as a symptom of myxedema. When rats are given a large injection of estrogen, the oxygenation of blood in their lungs is sharply decreased in less than an hour. Although it is not common to test oxygen diffusion in humans, I know of two women in the same family who showed very poor pulmonary oxygen diffusion after they were put on high doses of estrogen. (Since estrogen inhibits thyroid secretion, and hypothyroidism is associated with elevated estrogen, they should be considered together.) Leakage of proteins from capillaries in the lungs is probably responsible for the decreased diffusion, by thickening the layer through which the oxygen must diffuse.

When myxedema exists in childhood, the cartilage in joints swells, and is deformed, causing a characteristic knock-kneed appearance. In a milder form, the swelling can cause joint pain that doesn't involve the characteristic inflammation of arthritis. In a mild form, the calf muscles tend to swell after prolonged activity; the "growing pains" that are so common around the beginning of puberty are probably the result of a temporary hypothyroid edema of the leg muscles.

When a tendon swells, it is sometimes the result of a local injury or of a particular over-use of a muscle, and in these cases local treatment can sometimes produce a permanent cure. But when the problem keeps recurring, or keeps showing up in different areas, there is probably a general hormonal problem.

When a tendon in the wrist swells, it can cause numbness in the hand, by pressing on a nerve which passes through the carpal tunnel with some tendons. The tunnel is formed by a ligament that holds the tendons in place, and swelling of the ligament itself can contribute to compression of the nerve. Even the connective tissue that forms the nerve sheath itself can swell. Many people with undiagnosed hypothyroidism complain that they "have poor circulation," and that their hands and feet go to sleep easily. These are two separate (but related) problems that can be relieved through a nutritional and hormonal anti-stress program.

Low thyroid people often have cold hands and feet, and they often have nerves that are over-sensitive to compression. Poor oxygenation is involved in edema, both as cause and consequence. (I discuss this in more detail in "A Unifying Principle," chapter 7.)

Thus, swelling can cause compression and nerve injury in a way that is exacerbated by certain postures or repetitive

nerves and arthritis commonly follow treatment of the carpal tunnel syndrome by surgery or local cortisone injections. Glaucoma, a swelling of the jelly inside the eye, seems to result from a hormonal imbalance, since it can be relieved quickly by a natural hormone. Graves' disease, in which the muscles behind the eyes swell, can also be aided by similar treatments. In addition, "epilepsy" and symptoms ascribed to "multiple sclerosis" have been relieved by natural anti-stress and anti-edema hormones.

CHAPTER 15

THE PREMENSTRUAL SYNDROME

For at least 80 years, a syndrome of premenstrual tension has been recognized and considered to be the result of an ovarian hormone imbalance. As early as 1912, Armour & Co. was selling desiccated corpus luteum for use in cases of ovarian failure, and said that it "prevents nervous symptoms accompanying" menstrual abnormalities. (*New and Nonofficial Remedies*, 1912, Supplement, pages 158, 160.) It was also used to treat obesity and other physical conditions sometimes associated with "ovarian deficiency."

By the 1930s, when the specific ovarian steroids were identified, there was a clear consensus that estrogen and progesterone were involved in the syndrome, but there was some confusion over the question of whether the cause was high estrogen or low progesterone. It seems to have been French endocrinologists who pointed out that either high estrogen or low progesterone can cause the typical cyclic premenstrual symptoms, since it is the ratio of estrogen to progesterone which determines the nature of the physiological response. By the mid-1930s pure progesterone was on the market in the United States and Europe, and was widely used to treat problems of pregnancy, menopause, dysmenorrhea, and the premenstrual syndrome.

Although it has been only in the last 20 years that animal studies of the behavioral effects of the steroid hormones have become subtle enough to explain their role in emotions, depression, aggression, etc., the more physical dangers of

excessive or unopposed estrogen were clearly recognized by the late 1930s and the early 1940s: It was, for example, known to cause cancer, infertility and miscarriages, excessive blood clotting, edema and a shock-like stress reaction. Other toxic effects of estrogen--seizures, birth defects, toxemia of pregnancy, increased intraocular pressure, atrophy or necrosis of various tissues, etc.--continued to be discovered, while the opposing steroid, progesterone, was found to offer protection against these, and still other, toxic effects.

Although the premenstrual tension syndrome, in its behavioral and subjective aspects is now recognized as a significant (and treatable) problem affecting a very large proportion of women in their reproductive years, another very important issue is that the hormone imbalance which causes the premenstrual discomfort and disability also predisposes the sufferer to serious organic problems.

While both animal studies and human studies have shown that natural and synthetic progestins protect against estrogen-induced cancers, and some other diseases, only natural progesterone is recognized as having general value in the treatment of the premenstrual syndrome. This is apparently because natural progesterone has a broad spectrum of intrinsic effects, and is easily metabolized into other active hormones as needed, that is, it is a basic precursor substance. It has been tested in isolation on practically every type of tissue, where it seems to have a stabilizing action: nerve, smooth muscle, cardiac muscle, epithelial cells, cells of the immune system, etc. It is anti-spasmodic, anti-inflammatory, anti-mitotic in certain tissues, and (at high concentration) anesthetic. Its use before and during pregnancy has been associated with a lower than normal incidence of birth defects.

Although natural progesterone has a broad spectrum of action and is remarkably free of side effects, the use of natural progesterone has been limited by the expense and inconvenience of the forms commonly used. Some women continue to use suppositories, because they do offer some relief of symptoms, even though they are very messy, and they are necessarily expensive, since only 5% or less of their progesterone content can be absorbed.

Injectable progesterone is both inconvenient and expensive. The form commonly used contains 10% benzyl alcohol, as a solvent and as a local anesthetic, since progesterone is not sufficiently soluble in ordinary vegetable oil, and can be painful when injected as an aqueous suspension. However, benzyl alcohol has significant toxicity to nerves, and can produce anaphylaxis.(1) Benzyl alcohol, in contact with tissue, combines with water, causing progesterone to be deposited as crystals. Even if oils needed a "bacteriostatic agent," the quantity used with progesterone has no justification except as a solvent, but it is not described as such. The fact that injected progesterone has been beneficial, in spite of the neurotoxicity and instability of the solvent, is another illustration of the protective action of progesterone.

Micropulverized progesterone is expensive when taken orally, since it is poorly absorbed, and when absorbed it is quickly inactivated by glucuronidation, since it is exposed to enzyme action in the wall of the intestine itself and in the liver, if the individually absorbed molecules get that far before being inactivated.

Substances, even including peptides, which are absorbed by the chylomicron pathway, reach the general circulation without being exposed to the inactivating glucuronide-transfer enzymes of the intestine or liver. People often speak of

"avoiding the liver on the first pass," but in fact chylomicrons pass through the liver many times before they are destroyed; after an hour, 10% of the chylomicrons are still circulating. If progesterone is taken orally in oil in a truly solvated state, in a monomolecular dispersion, it will enter the blood via the protected chylomicron route. Merely mixing finely powdered progesterone crystals with oil will not allow it to enter as chylomicrons; the size of chylomicrons is very small. They are usually about 4000 Angstrom units in diameter.

Fats taken orally are almost 100% absorbed by the small intestine. Like other hydrophobic substances, progesterone will be absorbed by adipose tissue and by the brain, but, unlike other steroid hormones, it also tends to be absorbed by red blood cells. Typically, the concentration of progesterone in red blood cells is twice that of the serum.(2) (And the brain contains a still higher concentration.) These intracellular reservoirs of progesterone tend to prolong the elevated blood levels resulting from the absorbed chylomicron-progesterone, so that the observed hormone levels after a single oral dose are much more stable than are the triglyceride levels after a single fatty meal. Typically, after a single oral dose of 100 mg. of perfectly dispersed progesterone, a post-menopausal woman's serum progesterone level will still be in the "normal luteal phase range" 24 hours later. The difference in efficiency--and therefore in cost--between this form and the various crystalline dispersions is very large.

Natural progesterone therapy in the form described above remains the most direct and general treatment for PMS; thyroid and vitamin A, and other normalizers of mitochondrial respiration, such as red light and short chain saturated fats, act in the same direction. Fiber, bowel stimulants and antispasmodics, and broad spectrum bowel "disinfectants" such as flowers of sulfur, sodium thiosulfate, and short and medium-

chain saturated fatty acids, can contribute to alleviation of premenstrual symptoms (as discussed in other articles). Penicillin can also tentatively be added to the rational therapies for PMS, as a flora-normalizing one-time or occasional treatment, though I think the other methods are so effective that any need for penicillin would be rare.

My first suggestion for someone with PMS is to avoid thyroid suppression (diet; darkness and endurance exercise should be avoided), and to use my carrot salad recipe: Grated carrots, vinegar, coconut oil and salt are the essentials, garlic and olive oil are optional. Acetic acid and fatty acids released from the coconut oil act at different levels, and the carrot fiber is a timed-release system which also binds toxins and stimulates the bowel; the salt spares magnesium and tends to inhibit excessive prolactin release. Use of a balanced thyroid (Armour or Proloid) supplement can help to restore normal thyroid function by breaking the cycle of stress. If these methods aren't enough, progesterone or pregnenolone can be supplemented. Both of these help to normalize thyroid function, and both have the "catatoxic" function of protecting against a wide range of toxins.

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CHAPTER 16

RESTORING FERTILITY

Since my study of the role of oxygen in fertility, between 1970 and 1972, I have concentrated on working out the implications of what I observed, and have written very little about the treatment of infertility. But every time someone would mention that they were unable to get pregnant, I would explain what could be done, and they would get pregnant, usually within a few weeks. The trick is simply to normalize the use of oxygen, by normalizing everything related to hormones and nutrition.

AGE LIMIT CONSIDERATIONS

Several years ago, a friend of mine had a healthy baby a few months after she had begun using small supplements of hormones, and several years after her early menopause. I wondered whether age or the absence of menstruation might be almost irrelevant to fertility, if the right balance and sequence of hormones could be achieved.

A gynecologist I knew had been giving his wife progesterone since she was about 40, and at 60 she was youthful looking, and still menstruating. I have known of many women who still menstruated at 55, and--since diet and light and stimulation powerfully affect metabolism of hormones--it is easy to imagine that natural conditions could sometimes help to preserve fertility beyond that age.

A grave monument in St. Peter's Church in East Oxford records the death of a woman in childbirth at the age of 62.

The old medical and obstetrical journals have many reports of women who had children long after menopause.

Depasse (Gazette Medical de Liege, Oct. 1, 1891) described a woman who had a child at the age of 59 years 5 months, and who suckled the baby, and weaned it on her 60th birthday. Her menopause had occurred 10 years before the pregnancy.

The famous American physician, Benjamin Rush (in Medical Inquiries and Observations, Philadelphia, 1805) described a woman of 60 who had a child.

Wallace (Philosophical Transactions of the Royal Society of London, vol. xxii, Page 543) reported a woman on the Isle of Orkney who had a child when she was over 60.

There have been a few reports of children borne by women of 70 (L'Union Medical du Canada, Montreal, Dec. 3, 1881), and older (Mayham, in Medical Standard, Chicago, Jan. 1891).

There are a few accounts of even older women who had healthy babies, and occasionally a calcified fetus is found in the uterus of an extremely old woman during autopsy. The assumption that the "child-bearing years" end around the age of 50 has led to the conclusion that such fetuses have remained "in utero" for decades, but no one knows how long the calcified fetus can persist in the uterus.

Taboos undoubtedly influence the willingness of pregnant old women to tell their true age. Similarly, our cultures have tended to blame women for all reproductive problems. (In *Nutrition for Women,* I discussed some of the evidence that

birth defects are often the father's contribution, but since then the evidence in support of that view has become much clearer. Male geneticists used to have a little spiel which "explained" why women were responsible for Down's syndrome, etc., but it actually explained nothing.) "Everyone knows" that old men can produce children far beyond the age at which women become infertile. Our culture honors old men who can reproduce, and so the claims of fatherhood at a great age are likely to be more numerous than the claims of mothers that they are very old. I knew a man in his 80s whose pretty wife of about 30 had a baby, but not everyone believed he was the father. However, when a woman has menopause at the age of 47, marries a 22 year old man when she is 52, and has children when she is 53 and 54 (Cachot, in Pacific Medical and Surgical Journal, vol. xxvi, page 394, 1883-4), there can't be the same sort of doubt. In the latter case, one could assume that a young husband optimized the couple's fertility.

Since both parents are involved in reproduction, couples that want to have children must consider the health of both. Thyroid and pregnenolone and vitamin E are as important for male fertility as thyroid and progesterone and vitamin E are for female fertility. (For example, supplementary thyroid and pregnenolone can raise a man's sperm count, by overcoming the effects of stress.)

THE MECHANISMS OF FERTILITY

Since it helps to have information from blood tests, physicians are often involved, and it is important that both the woman and her doctor be aware of what the other is trying to do. For example, the thyroid hormone, triiodothyronine (T_3), is a key element in producing the energy needed for pregnancy to begin, but if there isn't enough cholesterol circulating in

the blood, it will be impossible to synthesize enough progesterone (and other steroids). Too much carotene, too little vitamin A, not enough magnesium or sodium, and too much cortisol are commonly overlooked factors in infertility.

It isn't uncommon for women to experience monthly periods several months into pregnancy; even when there isn't continued monthly bleeding, the cervical mucus test will often show that there is a cyclic monthly shift toward estrogen's dominance. These are times when the probability of a miscarriage is increased.

The most common time for miscarriages is at the ninth week. At this time (just as the placenta is about to take over the bulk of hormone production from the ovaries) there is normally a brief decrease in the ratio of progesterone to estrogen. The decreased ratio of progesterone to estrogen is characteristic of normal menstruation, and when it occurs during pregnancy, there will be either some degree of bleeding or a change in the structure of the mucus, if not a miscarriage. Estrogen lowers the availability of oxygen, and progesterone increases it. Bleeding is caused by changes in the blood vessel (spasm followed by dilatation) promoted by nerves, under the influence of estrogen and the resulting oxygen-deficiency. The rate and quality of fetal development is influenced by these hormone balances.

In animal experiments, an appropriate dose of estrogen terminates pregnancy at any stage. It is clear that lack of oxygen caused by estrogen dominance is a major factor in miscarriage at any stage. The six-day-old embryo suddenly becomes dependent on oxygen, just at the moment of readiness for implantation. Only a small excess of estrogen is needed to prevent implantation of the embryo, because progesterone is produced in relatively small amounts at that early stage, but

even late in pregnancy a dose of estrogen sufficient to override the effects of progesterone can destroy the fetus.

In smaller doses, estrogen damages the fetus without killing it, by stopping brain growth, for example. In the later stages of pregnancy, any slight oxygen deficiency causes an excessive use of glucose, as a partial compensation, and the resulting hypoglycemia can cause symptoms in the mother while damaging the fetus. Morning sickness, temporary blindness, fainting, and seizures are common effects of low blood sugar, especially after the fifth month, when the baby's brain is growing rapidly and consuming increased amounts of glucose.

Adequate protein, glucose, and sodium to maintain blood volume will prevent most of these problems of later pregnancy, unless the hormonal imbalance is very bad. Milk and fruit juice taken several times a day are usually helpful. Body temperature and pulse rate should be monitored, to see whether the metabolic rate is approximately normal. Sometimes, a single dose of progesterone can normalize a pregnancy, but both thyroid and progesterone should be considered for improving fertility and preventing miscarriage. Women who used progesterone before getting pregnant had babies with a very low incidence of congenital defects (roughly 1/10 the "normal" rate), and women who used sizable amounts of progesterone during pregnancy had outstandingly superior babies. The things which sustain fertility, in its simple sense, also are the things which optimize the life of the child.

PART THREE:

REGENERATING KNOWLEDGE

"As the true method of knowledge is experiment, the true faculty of knowing must be the faculty which experiences."

W. Blake

Our organism has requirements that must be recognized, and one of these is the need to know, to have intellectual adequacy. Knowing takes energy, and our experience is influenced by our biological state. We can improve our developmental conditions, socially and materially, to bring our species up to a higher level of mental energy. In this section, I discuss some of the biological, social, and ideological aspects of the problem--the problems of how to overcome inertia and foster creative knowing.

CHAPTER 17

YOUTH, ENERGY, AND REGENERATION

Being alive is good for you. But our culture is saturated with arguments to the contrary--that it is life which kills us, and self-denial which sustains us. It is always easier to blame the victim than to search for the real cause of a problem. In this chapter I will give some of the arguments in favor of life and more life, or rather, some of the evidence from which those arguments can be made.

Fifty years ago, Clyve McCay reported that restriction of calories in the diet increased animals' longevity. At that time, many biologists believed in an innate and universal "metabolic potential," according to which each gram of living tissue could produce only a certain number of calories of energy metabolically, beyond which it must decline and die. In Raymond Pearl's version, this limit was governed by heredity, and was originally demonstrated by showing that different individual organisms could survive total energy deprivation for different lengths of time; slow metabolism postponed starving. (Obviously, starvation has no logical connection with aging.) Later, Pearl argued that more intense activity accelerated aging.

There are now many people who argue that a low metabolic rate, a low body temperature and slow heart beat indicate that you should live a long time: "your heart can beat only so many times." Most of these people also advocate "conditioning exercise," and they point out that trained runners tend to have a slow heart rate. (Incidentally, running elevates

adrenalin, which causes increased clumping of platelets and accelerated blood clotting. Hypothyroidism--whether pre-existing or induced by running--slows the heart, raises the production of adrenalin, and is strongly associated with heart disease, as well as with high cholesterol.)

Early in the century, Alexis Carrell showed the importance of environmental factors in the aging process, by keeping chicken cells alive and functioning for many years beyond the chicken's normal life-span. In 1927, German researchers reported that a fat-free diet prevented the occurrence of spontaneous cancers in rats. Since, a little later, other workers found that the elimination of unsaturated fats from the diet not only prevented cancer, but also caused a large increase in the metabolic rate, it might have been possible to conclude that it is not living which kills us, but something in the environment. Some people did draw that conclusion, but research funds go mainly to product-oriented research, and "the environment" has been hard to package as a product.

Carrell's work involved frequent changes of the fluid that the chicken cells were growing in. Later, Hans Selye did an experiment in living rats that seems to relate to the importance of frequent changes in the growth medium. Selye implanted glass tubes under rats' skin, and found that they were soon encapsulated by fibrous tissue, and that a filament of tissue then grew down the tube, joining the membranes at the ends. When left undisturbed, this filament, isolated from the circulatory system, underwent very rapid aging.

But when Selye drained the fluid at frequent intervals, the age-changes were prevented, and even when the rats died of old age, the filaments still appeared to be young. Another gerontologist, who had an extremely old and decrepit dog, removed, a little at a time, the dog's blood, discarded the serum,

and replaced the cells suspended in a saline solution; the dog appeared to be rejuvenated, and regained all its normal functions. The blood serum from young animals or people supports better cell growth in vitro than does the serum from older individuals.

Two clear differences have been found between old blood and young blood. The albumin in old blood is in a more oxidized state. (I think it was the famous gerontologist, Verzar, who first reported this.) Although, at least in aging humans, there is much less oxygen in the blood, something causes the albumin to be in a more oxidized state in older blood. The other distinct feature of older blood might also seem paradoxical at first: the red blood cells are younger. That is, in an old individual, the red blood cells are more fragile--possibly from being more quickly damaged from oxidation--and are replaced sooner, and so, on average, they are many weeks younger than the cells in a healthy young individual.

Neither of these features is paradoxical. Poor oxygenation is a stress, and causes the waste of glucose and compensatory mobilization of fat from storage, and the relatively reducing environment in the cytoplasm causes the mobilization of iron from storage, in the toxic reduced (ferrous) form. Products of the peroxidative interaction of iron with unsaturated fats are evident in the blood (and other tissues) during stress, and especially so in older animals.

Several things relating to calorie-restricted diets are not generally known. First, in 1987, Schroeder found that the removal of toxic heavy metals from the diet had the same effect as caloric restriction. Second, although underfed animals grow more slowly, their metabolism is not necessarily depressed. (In fact, animals on a low protein diet have a higher

rate of oxygen consumption than do the animals that eat a more normal diet.)

Many older studies found that rats which were deficient in the "essential fatty acids" had the signs of hyperthyroidism, and were in a hyper-metabolic state. The avoidance of oxidatively toxic heavy metals, and the maintenance of respiration, with an absence of the highly peroxidizable unsaturated fats in the diet (and a lower level of them in the storage tissues) would probably make the animals tolerate stress better (EFA deficient mitochondria are more resistant to oxidative injury, and vitamin E prevents many stress-associated problems), and might inhibit the age-related oxidative changes in serum albumin, red blood cells, and other tissues.

A third finding related to dietary restriction concerns protein turn-over. One of the basic metabolic changes in aging is slowing of the rate of protein turn-over in cells, and it appears that dietary restriction enhances the protein turn-over rate in aging animals. I think it is likely that unsaturated fats and the amino acid, cysteine, both contribute to the age-related retardation of protein metabolism, but I don't think this has been directly tested yet.

(In reading the published research on dietary restriction and the effects of unsaturated or saturated fats, it is important to pay careful attention to the actual composition of the diet. The cancer rate, for example, usually reaches a maximum and levels off at a corn oil content of less than 10% of calories, but this content is often called a "low fat" diet. If a normal and low calorie diet both contain 6% corn oil, which is clearly carcinogenic, the animals which eat less food will eat less corn oil, and will also tend to burn it more completely for energy, so there will be a major difference in the toxic effects of oil. Lard is often the same as soy oil in linoleic acid content, yet it

is too often described as a "saturated fat." I read a publication on the effects of a "low fat" diet, which contained 20% corn oil; sometimes I feel there is a deliberate attempt to mislead when language is used so arbitrarily.)

Besides the observation of greater oxygen consumption in the low fat animals, and high protein turn-over in calorie restricted animals, there are observations in a variety of organisms associating a higher metabolic rate with greater longevity. While most longevity studies of flies involved altering the temperature of their environment, studies of differences of metabolic rate at a given temperature have in several cases found greater longevity in the high metabolizers. A study of 18 strains of mice found a clear association between a higher metabolic rate and greater longevity.[1] Recent studies (e.g., Joseph Graves') are showing similar associations in insects.

Sacher popularized the idea that a larger brain is associated with a longer life span, and others more recently have refined the idea in connection with body size, index of cephalization, and metabolic rate. For example, M. A. Hoffman ("Energy metabolism, brain size, and longevity in mammals," *Quar. Rev. Biol. 58*(4), 495-512) said "...it has been shown that the ratio of cortex-to-brain metabolic rates is independent of body size, and increases with the evolutionary level of brain development." (Figure 1) It is interesting to consider that birds generally live longer than mammals of the same weight, though their brains are usually smaller, and their body temperature is several degrees warmer. Among birds, parrots and other relatively large-brained birds have an extremely long life span, compared with mammals of the same body size. For example, a rat lives about 2 years, at 98 degrees F., and a medium sized parrot lives about 70 years, at 104 degrees. According to H. Rahn ("Time, energy, and body size,"

chapter 16 in *Environmental Physiology*, editors C. V. Pagenelli and L. E. Farki, Springer-Verlag, 1988), the total energy per gram of tissue per life span is about four times higher in passerine birds than in mammals.

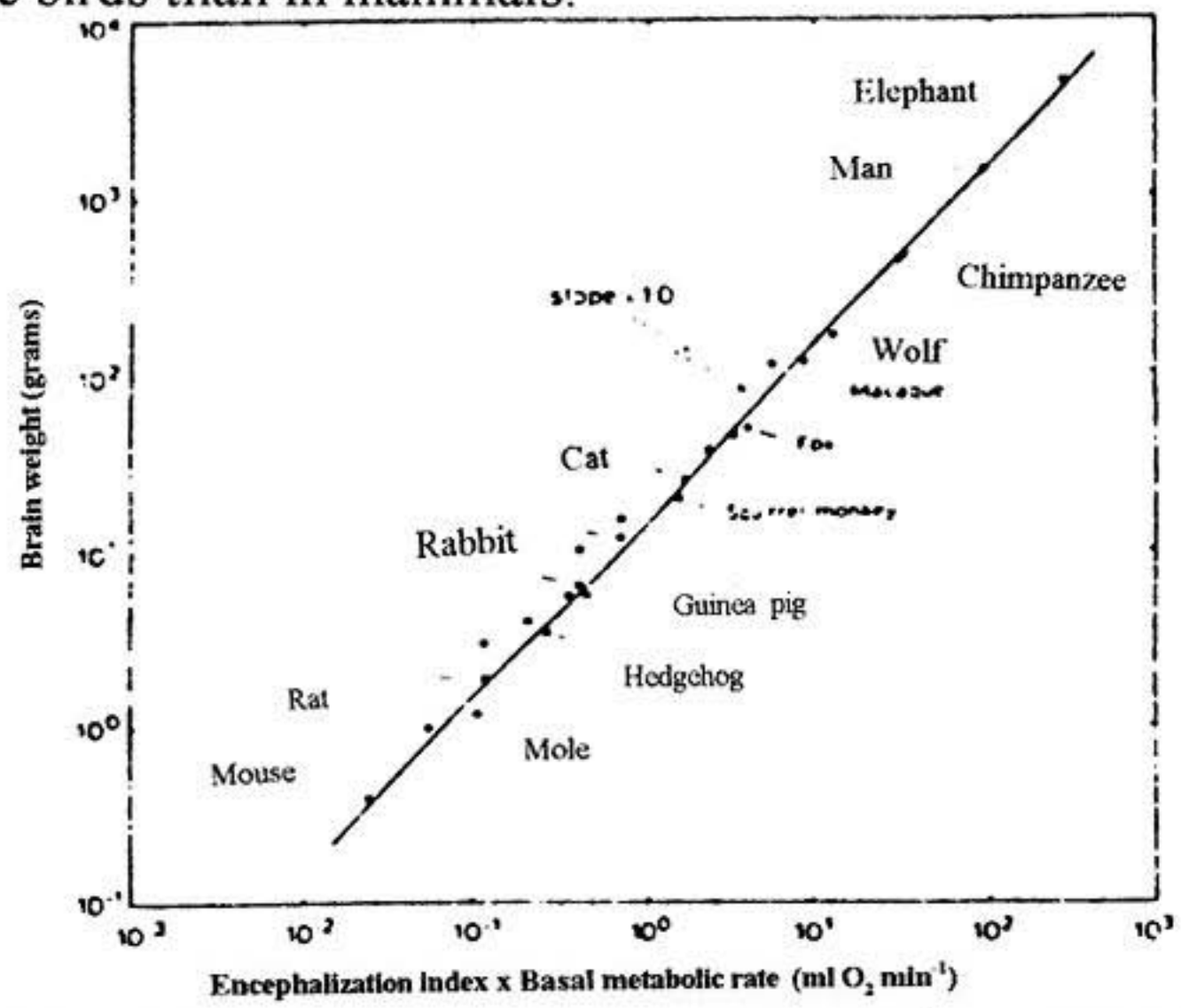
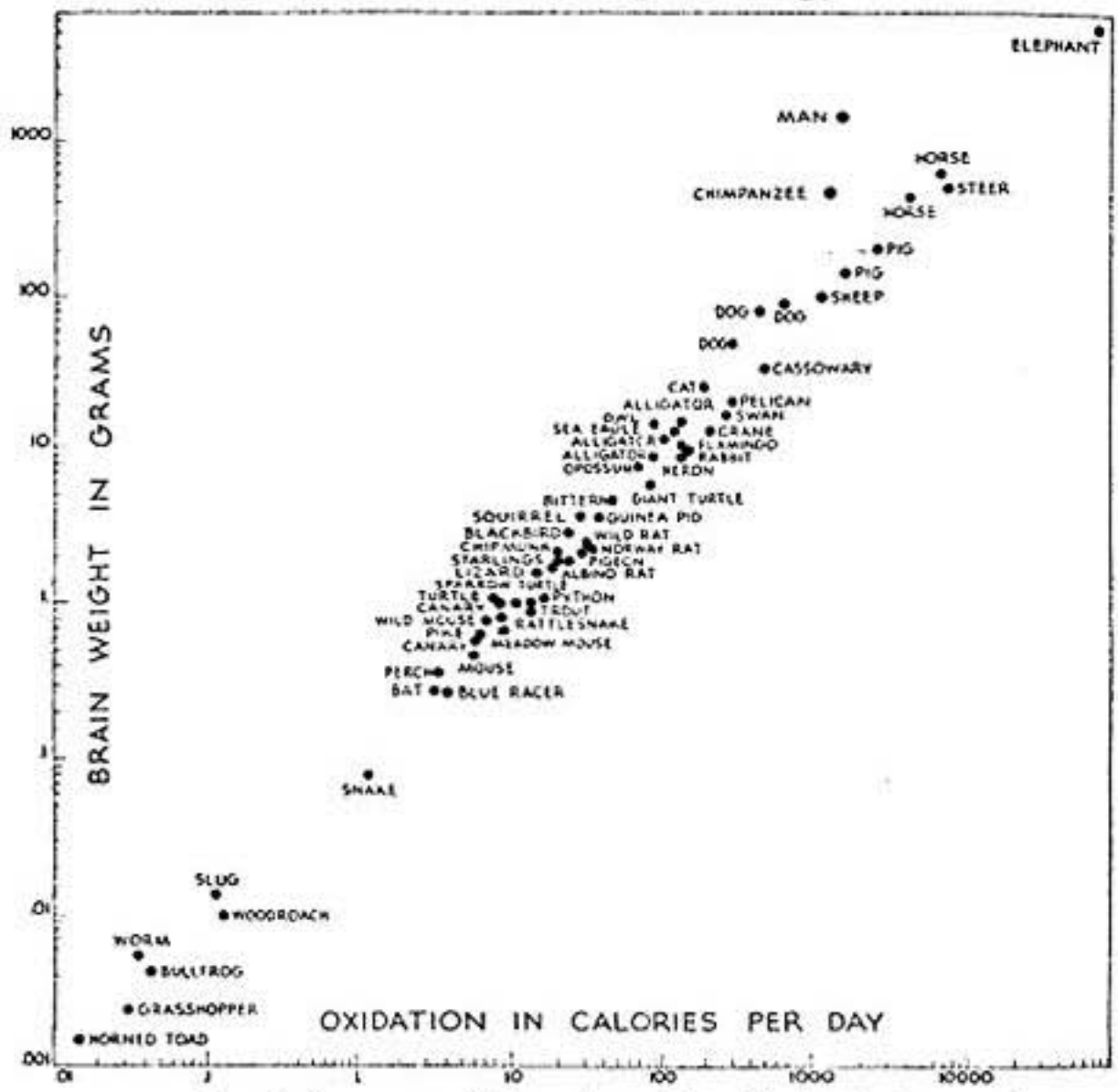


Fig. 1, Hoffman: "Enlargements of Brain Size Keep Pace With The Availability of Energy"

Fig 2, Crile:



—In relation to metabolism the weight of the brain shows a law.

Undoubtedly, he meant us to infer that these "uncivilized" people fell on the same line as animals, because their brains lacked the cultural quiet parts. My interpretation is that they ate traditional diets, rather than the grain-based diet of the United States and Europe which suppresses brain metabolism, in the same way that the "normal" animal diets suppress metabolism (and decrease longevity). Many researchers (before the late 1940's) found that about 40% of the people in the U.S. showed evidence of deficient thyroid function (low oxygen consumption and high serum cholesterol), and benefitted from taking a thyroid supplement. Cancer, heart disease, and high susceptibility to infections were found to be extremely prevalent in populations with subnormal thyroid function.

Low thyroid function, relative over-feeding, and the presence of unsaturated oils in the diet are known to accelerate sexual maturity. Early sexual maturity has been associated with premature aging and early death. Fish, octopuses, mice, humans, and plants offer examples in which reproductive maturity initiates the aging process. Although it used to be said that "hot tropical" people had early puberty, and "cold northern" types had late puberty, the best available data contradict that opinion. The oldest averages for the occurrence of puberty occur in tropical regions. (Figure 3)

Mere calorie restriction can delay puberty (and this usually means a low fat diet, for poor people in the developed countries) as can be seen in data from Appalachia; late puberty, accompanied by very low birth weight for babies, is the typical pattern of poverty. Given enough fat (especially vegetable oil, including that in beans and corn), harsh conditions can probably cause earlier puberty, but I don't know of any clear evidence on this subject.

In the tropical regions where puberty doesn't occur until about the age of 17, it seems that some of the heaviest birth weights occur, and high birth weight generally indicates good maternal nutrition. (Figure 4) These tropical areas generally coincide with areas where coconuts are produced abundantly, and are used for food. Animals fed coconut oil are lean, have delayed sexual maturation, and have offspring with larger brains than animals fed similar amounts of unsaturated oils. Since coconuts and related fruits contain sterols, their use might have a direct hormonal action, in addition to the effects of the easily metabolized high energy short and medium-chain fats, which support an efficient and intense respiratory metabolism. The dietary hormones are probably responsible for the high metabolic rate of the Eskimos, too, except in that case glands, skin, and brains are regularly eaten. Tropical people generally consume all parts of their food animals, too (except for vegetarian cultures such as Hindus, which use only milk and butter from their cows), though the Eskimos are unique in having, traditionally, a pure meat diet.

W. Donner Denckla suggested that there is a "death hormone" in the pituitary gland, which appears at puberty and initiates the process of aging by suppressing the use of oxygen. He maintained that merely providing thyroid supplement wouldn't protect against it, and that it was a distinct hormone, although it tended to appear in tissue extracts in association with prolactin and growth hormone. Although I think there is still a lot to be learned about the pituitary hormones, I don't think Denckla discovered anything except puberty.

The sex hormones--especially estrogen--are closely involved with respiration. My dissertation, "Age-related oxidative changes in the hamster uterus," surveyed some to the same information. Estrogen and prolactin do many things to interfere with respiration. L. C. Strong, who developed

strains of mice with high estrogen and a tendency to die of mammary cancer, found that early sexual maturity was associated with a shorter life-span. Similar observations have been made in humans.

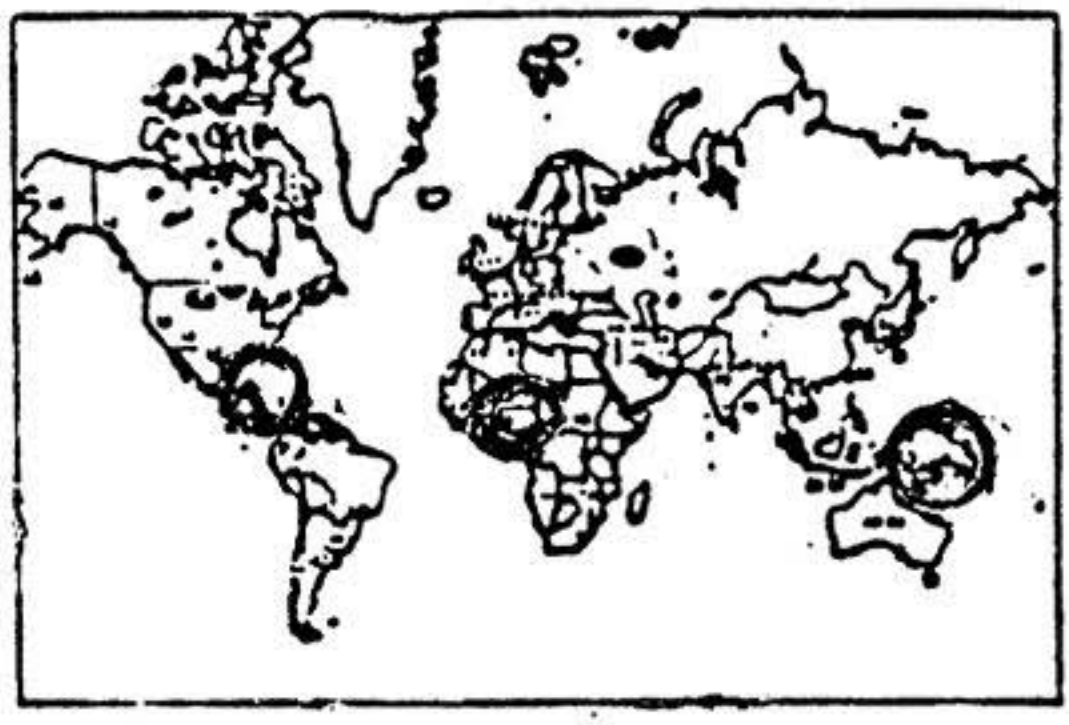


Fig. 4 - Birth Weight
Caribbean, Central Africa and New Guinea have the heaviest birth weights in the world: 3.4 kgs.

Fig. 3 - Age at Puberty
Caribbean: 15.1 years; Central Africa: 16.5 - 17 years; New Guinea: 15.5 - 18.4 years

Rather than supposing that we contain a system for self-destruction, I suspect that reproductive maturity appears at a time when the organism is experiencing a generalized, life-threatening metabolic stress--namely, aging--and that the metabolic slowing which begins at puberty signals the appropriateness of reproduction, and makes the organism more dependent on the glucocorticoids (regulated by the pituitary). The accumulation of iron, unsaturated fats, and other toxins, I think, are major signals for puberty. (Specifically, factors which inhibit cytochrome oxidase.)

Marion Diamond, who studied the effects of stimulation on rats' brain development, found that pregnancy or progesterone treatment--like freedom and stimulation--caused the brain to grow, and estrogen--like stress--caused it to shrink. The larger-brained animals had smaller faces, and the confined, stressed rats had smaller brains and bigger faces. (I see no reason to doubt that human proportions are similarly influenced by prenatal stress; Franz Boas, for example, found that immigrants' childrens' head shapes were similar to head shapes in the new country, and unlike their parents.') These changes are similar to the differences between small-faced babies and large-faced adults. The observation that the babies of one species resemble the adults of a more highly evolved species has led to the idea of evolution through neoteny (or paedomorphism or juvenilization), in which juvenile traits are preserved for a longer time in the offspring, and eventually persist even after reproductive maturity is reached.* The same terms are sometimes used in describing plants, as well as animals.

Some feminists have objected to the characterization of female traits as "paedomorphic," considering it as another attempt to deny women equal social status with men. It was common for Ashley Montague's book, *Natural Superiority of*

Women, to be condemned by "feminists" as "patronizing." Nevertheless, I think it is a mistake to argue for a kind of biological relativism (analogous to cultural relativism) which avoids the idea of a possible evolutionary significance in certain biological features.

If a certain substance, such as progesterone, closely reflects the quality of environmental support and is intimately involved in realizing and sustaining our most characteristically human evolutionary features, I don't think we should deny its importance just because of its greater importance in women than in men. Progesterone's effects are "neotenous," in the sense of prolonging youthful traits. Women have several "neotenous" features relative to men, including a bigger ratio of brain to lean body mass, a smaller face-to-cranium ratio, differences in voice and body hair, less aggressiveness, and greater adaptability. (In spite of the people who teach assertiveness, I think high adaptability and low aggressiveness are characteristic human and primate traits, which are typical of infants, and are likely to represent our species' future.)

H. G. Wells wrote that

> *"The creature called Homo sapiens emerges from among the earlier Hominidae, very evidently, as another of these relapses of the life-cycle towards an infantile and biologically more flexible form which have played so important a role in the chequered history of living things. He is not the equivalent of the clumsy adult Heidelberg or Neanderthal man. He is, in his opening phase, the experimental, playful, teachable, precocious child, still amenable to social subordination when already sexually adult. The ever-changing condition of life had less and less tolerance for a final gross, overbearing adult phase, and*

it went out of the cycle. . . . . .the now unnecessary primordial adult Homo, for all effective purposes, faded out, leaving as his successor the childlike Homo sapiens, who is, at his best, curious, teachable and experimental from the cradle to the grave.

...It is possible that the mass of contemporary mankind may not be as readily accessible to fresh ideas as the younger, more childish minds of earlier generations; and it is also possible that hard imaginative thinking has not increased so as to keep pace with the expansion and complication of human societies and organizations. That is the darkest shadow upon the hopes of mankind.

There is no way out for Man but steeply up or steeply down."

A high level of metabolic intensity is characteristic of both young plants and young animals under conditions that are ideal for their life, meeting their energy and substance needs abundantly. Both plants and animals are able to adapt--phylogenetically and ontogenetically, i.e., through both transgenerational and developmental changes--to marginal conditions of energy and substance availability.

The term "paedomorphic" has been applied to plants which preserve the "youthful" pre-reproductive forms for extended periods. Premature reproduction can be produced by stress, or to look at it from another angle, the conditions which prolong the growth state can be thought of as stress-free conditions. (R. Criddle and L. Hansen, in *Plant, Cell, and Environment*, report that a plant's metabolic rate, measured as heat production, can predict its future growth rate. Jerry Barnes, a tree developer in Cottage Grove, Oregon, discovered several years ago that the intensity of the metabolic

activity even in seeds can be used to accurately predict the future performance of the tree, cutting many years out of the process of tree improvement. The story of how his work was received at the state university is interesting; he did some quick lab tests on seed provided by the university, and they confirmed that he had correctly chosen the seeds which produced the best trees in their 13 year study, but they simply rejected his result as not conforming to accepted ideas.)

According to Jerry Barnes' theory, trees become able to move into less favorable niches by accumulating "restraint genes," which limit their growth, but prevent death by making them able to tolerate marginal conditions.** The theory of Criddle and Hansen seems to be similar, in looking for a stable metabolic rate when the plant is subjected to stress.

Upward adaptiveness, which is typical of large-brained animals and of plants with a high metabolic rate, allows the organisms to find more expansive niches by living at a higher energy level. This process obviously places great importance on an environment which can provide abundant energy and the necessary nutritional substances.

The fact that steroids seem to be made by all organisms except viruses, and are often identical in very different organisms (e.g., estrogen in yeast is exactly the same as human estrogen), has led me to experiment with "animal" hormones, such as progesterone, on plants. I think the systematic effects on "gene expression" and biochemical functioning that steroids are known to have in animals can also be seen in plants.

Producing energy abundantly, and using it efficiently: This seems to be an important effect of certain steroids. It might amount to a kind of by-passing of the "restraint genes." The kinds of changes which can be induced by hormones can also be inherited.[2]

If we optimize the known factors which improve energy production (red light, short-chain and medium-chain saturated fats, and pregnenolone, for example), to the extent that our metabolism resembles that of a ten year old child, I don't think there is any reason to suppose that we wouldn't have the regenerative, healing abilities which are common at that age. I suspect that both brain growth and remodeling might proceed indefinitely.

There is evidence that the cranial volume grows into old age, and also that the DNA content of the brain keeps increasing during adulthood. Presumably, this is only the result of an increase in connective tissue cells, but the certainty many people have that we can't grow new brain cells at any age is unfounded. Heart cells can now be made to multiply *in vitro*, and probably *in vivo*.[3] There is also some evidence for regeneration of brain cells *in vivo*,[4] and in birds brain cells have been found to grow new each spring in a part of the brain concerned with their singing, under the influence of a hormonal change. If the brain normally added a significant percentage of brain cells during adult life, the chance of finding a dividing cell by microscopic examination would be so small that we can't take the present absence of evidence for an increase of brain cell number during adulthood as having any meaning. The old doctrine, which claimed that "100,000 brain cells die every day," is now recognized to have no basis in fact.

For example, Bigl, *et al.* (*J. of Gerontology 33*, 172-180, 1987, citing the work of H. Haug, "Are neurons of the human cerebral cortex really lost during aging? A morphometric examination," in Traber and Gispen, *Senile Dementia of the Alzheimer Type*, Springer, 1985) say ". . .it was demonstrated that an age-dependent embedding-shrinkage of brain tissue together with a secular acceleration in body size may

significantly affect morphometric evaluation of neuronal densities during aging, and the view of a general neuronal loss during aging had to be corrected."

Rather than a programmed or random continuous loss of cells, when atrophy of the brain occurs, it seems to be caused by specific conditions, such as stress with prolonged exposure to glucocorticoid hormones. While estrogen is still sold for "estrogen replacement therapy" of menopausal symptoms, the typical symptoms of menopause (such as osteoporosis and hot flushes) can be produced by cortisol, and it is clear that these symptoms coincide with loss of the protective steroids such as progesterone, and not with a deficiency of estrogen.

The skeletal changes (shrinkage, curving of the back, moving forward of the lower jaw) which are so characteristic of old age in humans, also occur in other animals in aging and under the influence of the stress hormones. Since the protective hormones depend on the ability of mitochondria to convert cholesterol into pregnenolone, it is clear that damage to mitochondria will affect our supply of protective hormones at the same time that our energy supply is failing, forcing us to shift to the atrophy-producing stress hormones, including cortisol. Simple factors which protect the mitochondria are known to have profound therapeutic effects. At a certain point, I think we will understand mitochondrial protection well enough to prevent and cure the basic pathologies of aging. The Mayans and Eskimos studied by Crile produced 25% more biological energy at rest than people in the U.S. and Europe. They are culturally and nutritionally very different from each other, but they have enough in common to make them very different metabolically from the Euro-American culture. What they have in common is possibly something as simple as the absence of thyroid-inhibiting substances in their diet.

I think it is likely that our present knowledge of mitochondrial protection could give the average adult about a 50% increase in biological energy. To go beyond that level, it might be necessary to start at an earlier age, to allow body proportions to develop appropriately. For example, to handle a doubling or tripling of basal metabolic activity, a lung capacity of four or five liters would probably be needed. Like people who grow up in the high Andes, lung capacity would develop in proportion to need. (Incidentally, such a change occurring in most people would add billions of liters of water per day to the atmosphere; the average person vaporizes about a liter per day.)

The thymus gland is extremely sensitive to stress, and atrophies quickly under the influence of cortisone or the sex steroids, but it can also regenerate under the influence of thyroid and progesterone (and under some circumstances, probably DHEA) or just good nutrition. Chronic atrophy of the thymus produces immunological weakness. Infectious diseases, then, are not so different from the degenerative diseases, since the failure of biological energy, and the resulting stress response, can be responsible for both classes of sickness. Even radiation damage, which seems like a fairly exotic problem in comparison to infections and aging, is ameliorated by things, like thyroxin, which increase energy production (Timchenko and Antipenko, "Conditions for the use of thyroxine as an antimutagen after total-body x-irradiation," *Radiobiologiya 21*(2), page 204, 1981).

Since the DNA repair process is energy dependent, greater biological energy prevents mutations. It used to be a common belief among biologists that the "wear and tear" of being alive would cause mutations, as well as other cell damage. However, many lines of evidence show that stress and energy depletion are common causes of chromosome damage.[5] Even free

radical damage, which is popular as an explanation for aging, tends to become worse when energy is deficient[6] (fasting or emotional stress, e.g.), and not as a result of living itself.

Ideas of "original sin," "karma," "bad genes" or "wrong consciousness" are often invoked to "explain" suffering and disease. The most offensive example of this that I have heard was when a well known writer and lecturer claimed that people who are raped or murdered, even the victims of Auschwitz, including children, were responsible for their fate, through some mysterious spiritual defect. Even most of the conventional theories of aging and degenerative diseases contain a strong tendency to blame life itself as being at fault for its suffering.

Szent-Gyorgyi, in discussing some of his experiments with heart muscle, said "function builds structure, which increases the capacity for further function." The flow of energy through substance increases the order in that substance. More life and more energy can solve many of the basic problems of life.

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NOTES:

* "The breeding rate is found to vary with the increasing scope and degree of care from parents. The decrease in the number of eggs and young is associated with a higher nervous

organization expressing itself especially in intelligence, and helplessness is made concomitant with intelligence as its necessary condition." P. E. Davidson, p. 68 in *The Recapitulation Theory and Human Infancy,* Teachers College, Columbia University, 1914.

** "Vernalization" of grains might be thought of as suppression of neoteny, or activation of "restraint genes."

CHAPTER 18

THE TRADITION OF TRUTH

Several years ago I was thinking about the different levels of ability among famous painters of history, and I read about the family origins of some of them; the painters that I considered to have the best ability turned out to have come from poor families, in which skill in a craft was accepted as the way to earn a living. The bad--but famous--painters had "noble" origins, in which there was no tradition of skilled work. Painters who were "insiders," familiar with the attitudes of the rich who paid for the pictures, knew what things would flatter, what things were fashionable, and what would contribute to prestige. The people from a lower class, however, had to be very skilled at painting if they were to succeed.

I think this illustrates something general about truth. A person's vitality is drawn forward by meaningful work, that is, we grow to meet the demands of an important opportunity. Frans Hals' paintings could only have been done by an alert mind, and one which had been alert for a long time learning the skills of drawing and painting. That skill revealed a large amount of truth. On the other hand, from Rubens we don't learn much except that rich people ate well and dreamed of grandiosity.

William Morris said, "It is workmen only and not pedants who can produce real and vigorous art." I think something similar should be said for science.

While some people explore and solve important problems, others do not explore, and even reject solutions to problems

when they are made available by the workers who produced them.

One of my recurring objects of thought has been the slowness with which raw knowledge is assimilated. For example, I have been thinking about Broda Barnes's work on the prevention of heart disease with thyroid extract. He did solve much of "the riddle of heart attacks," but recent statements by the Heart Association show that the dominant forces in the health business haven't learned anything at all from his work, which be began 50 years ago. His work is clearly presented, not hard to understand, and it is scientifically so sound that no one challenges it, at least not on the scientific level. It is ignored, rejected by people who choose not to be bothered to read it. How many people have died from heart disease, since his work first became available? (And how many more from cancer, tuberculosis, and other diseases he showed occur mainly among hypothyroid people?)

I suggest that the resistance to Barnes's discoveries (and to nutritional therapies, etc.) has this explanation: that the health business is a Rubens-equivalent. There may be a family tradition of practicing medicine, but the child experiences family status long before he can experience the work of healing or the learning of special skills. Rather than an apprenticeship, it more closely resembles inherited nobility. Consider the character of most of the people who choose the profession, their motives, the way they are instructed, the meaning of truth in their lives.

But a few individuals within the profession live their lives for a different purpose, or cluster of purposes. They don't choose their problems in the way most likely to draw the favor of the powerful. Rather, there seems to be a need to understand, to take actions which lead toward the truth. I

suspect that an "apprenticeship" has somehow been served in most of these cases.

Seen from a distance, it may seem that such people know in advance where the truth is, so they can proceed in the right direction. Deep involvement in the problem, investment of some of your life in the work, reveals that the truth is everywhere, and is clarified and arranged through the technical actions of the worker. The production of (or "discovery" of) truth is nothing mysterious, as most philosophers and some scientists would have us believe.

In the Spanish culture in which Picasso grew up, there was the category of "genius," and Picasso clothed himself with the attributes of genius; he fulfilled his father's expectations, believed that he was that, and found a culture willing to believe it.

At that point, he could do no wrong; everything he did was the work of genius--"look at him, every scratch he makes with a pen is a stroke of genius." Criticism becomes impossible. The mystique around medicine is very similar. The public isn't qualified to criticize, and members of the profession are reluctant to criticize, because the myth must be preserved.

All the sciences, the military, and the activities of many politicians (the mystique of anti-communism in particular) propagate a way of living which just finds truth irrelevant. Mention "truth" in a roomful of scientists and you will hear a roomful of hoots and jeers, as if God had just walked to the podium at an atheists' convention.

But some people do take truth seriously, and a few try to find the "secrets" of people who have had it abundantly. Wilhelm Reich felt it had to do with a right relationship to the body and its energies; Einstein identified it with one's life.

Robert Creegan, in *The Magic of Truth*, tries to clarify its nature, and to reveal where it is in our life. The physiologist Ukhtomskii was interested in the same problem, what it is that allows some people to directly see the important truth, while others are concerned only with self-assertion. Describing one kind of clear perception, Ukhtomskii says, "I learned that it is created by a great physical effort, a tradition handed down from others, and an attitude toward the world as toward a beloved, respected companion with whom one is close to the point of intimacy." He says "it is only via culture in the whole man, the culture in his deeds (will and love) that a vision can be achieved. . . ." Tradition, effort, attitude, and culture--I will be saying more about these later, in connection with meaningful work.

Creegan tries to say the same thing Ukhtomskii said 40 years earlier; some of his statements are worth quoting, just because he is a contemporary American. "The best way to assert that a step is possible is, more often than not, just to take that step." "It may be shown that all human effectiveness involves a special exhibition of truth." ". . . A plenitude of truth in action belongs to the fullest, most effective living." "The social reinforcement of unimaginative living, however, tends to restrict and retard the advancement of science itself." "Intellectual achievement is facilitated by exercises directing imagination away from obsessive channels." Rather than abstract exercises, Creegan might have considered the beneficial effects of meaningful work.

The Indo-European civilizations were formed by conquering many other, older civilizations about 3500 years ago; the survivors in the conquered cultures effectively became slaves, useful workers. Long after the Romans had conquered the Etruscans, they returned to the north and conquered newer European cultures. The productive cultures kept some of

their roots, because that is where their usefulness came from--their ability to do things well enough to sustain themselves and also the conquerors. The Romans busied themselves with military processes and record-keeping.

All of the European civilizations had a similar internal division; at first different languages made the separation most obvious, but even after a kind of cultural unity had been imposed, the separation of productive and governing classes persisted. Sometimes the cycle was repeated several times (as in England), but always with the same overall outcome--if people were not highly productive, they were not worth conquering and enslaving.

Keeping this in mind, we can look at all kinds of cultural products, and see the results of this social division. In physics, we can compare the experimental attitude of Michael Faraday, the blacksmith's son, with the pompous errors of Lord Kelvin. In literature and the other arts, the richness of immediacy and realism in certain works distinguishes itself from the self-assertive fantasies and status obsessions of other works.

William Morris pointed out the similarity between the culture of the Romans and their subjects, and the culture of the workers and capitalists of his time, and he observed that these types expressed themselves in their art and science as different mental types. The productive people were described as constructive minds and "eye" people, or as "visionaries and practical people," whose work would be characterized by sensuous realism. The ruling classes he described as having analytical minds, concerned with formulas, labels, abstractions and theories, or formalisms.

Creegan and Ukhtomskii wrote about the two attitudes--full living vs. status concerns--and Morris observed that there are two cultures, sustaining those two attitudes, and showed

the importance of recognizing their products all around us, so that we can learn to evaluate them, according to their origins and their purposes.

Our intelligence develops as we grow into the world, such as it is, and our world includes things that we learn about, and the people that we learn from. As we learn our language, we are learning the knowledge, the abilities, of the people who use that language. That is the culture that we learn, and it may contain elements that are true, useful techniques, and other elements which stunt us, negate our curiosity, or turn us back from the world.

Philippe Aries, in *Centuries of Childhood,* showed that "childhood" is a modern phenomenon, that children used to be thought of as little adults. From an early age they participated in the work of the family, and the life of the society. (Some related ideas are discussed by Jerome Bruner in *The New York Review of Books,* Oct. 27, 1983.)

If children are isolated from any intelligent work that the parents may perform, the world that they learn is one of functionless entertainment. Any tradition passed down by their parents is one of attitude, rather than of ability. If the child is allowed to be present when the parents work, the child wants to participate, to help, and to the extent that the children can participate, they are apprentices, and they learn effectiveness, personal power. If they are not apprentices, they still adopt the world of their parents as it is present in their speech, and they may receive a sense of power, but in this case their experience is that to *belong* is enough to be effective, that they "deserve" status. And if they don't receive this inherited sense of status, they may inherit helplessness.

If work is removed from the presence of children, how is the enabling truth which is in our culture to be distinguished

from the useless aspects of the culture? If we lack a tradition of skilled work, then the point William Morris made becomes essential--we have to learn to reject the bad which is present in all the products of our culture--literature, painting, science, and so on.

To illustrate the double nature of our science, I will contrast two French scientists, de La Mettrie and Descartes.

Thinking of several kinds of biological facts, including the intrinsic motility or irritability of the intestine and heart, and the regeneration of the hydra from small fragments, Julien de la Mettrie proposed a new kind of physiology, based on the idea of organization. He suggested that thought was as natural for an organ with the structure of the brain, as beating was for the heart. He considered thought to be perfectly compatible with organized matter, and "to be apparently one of its properties--along with Electricity, Mobility, Impenetrability, Extension, and so on. . . . No: there is nothing base about Matter, except to those crude eyes which fail to recognize her in her most brilliant creations; and Nature is an Artist of unlimited capacities." He said that we should welcome our *natural* status, "cherishing life, scarcely understanding how feelings of disgust can taint the heart in this home of delight." (Compare Ukhtomskii's statement quoted above.)

One of de La Mettrie's physiological observations has been verified by recent experiments, nearly 250 years later--he noticed that his thoughts were quicker when his pulse was accelerated by a fever.

According to Toulman and Goodfield (*The Architecture of Matter*), it was de La Mettrie's uncompromising materialism that caused his (truthful) physiology of organization to be forgotten by the scientific tradition, while Rene Descartes' double reality--mind and matter as separate substances, interacting

only in humans, and there only at one point, which he thought might be the pineal gland--allowed him to compromise with religious beliefs. ". . . There had in fact to be a compromise; and the terms of this compromise have deeply influenced the subsequent development of science. Even today, their mark is evident in the structure of scientific ideas and institutions." (Page 165.)

For Descartes, science shouldn't mess with either God or the human mind. Theories about nature, including animals, could not refer to mentality. The traditional Christian sense of disgust for the body and matter had its influence on Descartes (and on the scientists who still follow his doctrines), but it was explicitly repudiated by de La Mettrie.

Above I have said that involvement in work orients a person toward the truth, that is, your "hypotheses" grow out of experience with the subject matter. Descartes explicitly claimed that it didn't matter how you choose your hypothesis: "Even supposing that I had assumed these principles at random, without having had reason to be convinced of their soundness, there would still be as good reason to suppose them the true causes of all that I have inferred, as in the case of a code deciphered by guesswork." A more perfect example of Morris's "theoretical" type would be hard to find. I don't know anything about de La Mettrie's childhood, but Descartes' father was a government official. I could give many contemporary examples, but these people were important in the history of philosophy and science, and they illustrate that both substance and method of science will vary systematically according to one's attitude toward the world.

If more scientists felt toward the world as La Mettrie and Ukhtomskii did, there would be not only a different "science," but a different world. "Nature is an artist of unlimited

capacities," but such art is invisible to those who consider science to be a matter of decoding a message written once in dead matter.

THE FUTURE OF WORK

Several years ago, in the quarterly publication *Social Sciences,* I noticed an article by a man whose specialty was exploring the future of work; he projected a future in which a person's desire for growth and exploration is realized in his work. This person's job was to clarify the changes that must be made in the "economy" so that it will serve humanity--the workers and consumers--instead of vice versa.

Previously, in *Mind and Tissue,* I had briefly discussed some Soviet views on labor: That work tends toward perception, as machines become available; politics, work, culture, and science interpenetrate; brain function, education, science, and work have much in common--an emphasis on purpose and goals, deep reorganization, and complex perceptual interaction with the material. P. K. Anokhin and A. A. Ukhtomskii, and their students have created a sound basis for the role of goals and future thinking.

The attitude toward the future is an important part of how we orient ourselves and what concrete things we do to prepare for the future. A mechanistic view argues that we can't intervene to change the future, that it must fundamentally resemble the past, and that if people just invest in things that promise to give them a good profit the future will be nice. Another view sees the future as being composed of choices which lead to new choices, with new possibilities emerging as choices are put into action.

It's important that people start talking about the possible choices we have. If we accept that "the choice" is between being unemployed and having a job, the job we get is not likely to be what we want to do with our lives. And "status" isn't what I'm talking about. Giving maximum meaning to our lives should be one of the basic things that we demand of our work.

1. To start with concrete and familiar things, we might first want to discuss what work is, and why--under capitalism, and also under fascism, primitive cultures, and socialism. The issue of specialization could be considered here.

2. This might be followed by considering what work could become, and how. The nature of history, time, and culture should be considered, as well as the projections that are made by different groups.

3. And at some point, I think it is important to consider how work shapes us, how we are our work, and why it defines what we can be. Cultural, intellectual, and biological influences should be considered.

There are some things I want to quote, because they suggest some of the things that work is, what it does to us, and what it should be.

About 1790, William Blake wrote the poem "London," which begins

> "I wander thro' each charter'd street,
> Near where the charter'd Thames does flow,
> And mark in every face I meet
> Marks of weakness, markd of woe.
> . . . .
> . . .the mind-forg'd manacles I hear."

Another poem, "The Human Abstract," begins

"Pity would be no more
If we did not make somebody Poor. . . ."

Repeatedly, Blake tried to define the mechanisms of oppression and limitation of the human personality. He observed that the State chartered corporations, licensed power; that it used false science, devious moralizing and religion, and illiteracy to create a culture of obedient drudgery. Commercial interests, he pointed out, distorted and degraded human life, art, and science.

> *"Schoolmaster of souls, great opposer of change, arise! O how couldst thou deform those beautiful proportions Of life & person; for as the person, so is his life proportion'd."*
>
> *"Thy self-destroying, beast form'd Science shall be thy eternal lot."*

Blake referred to factories as the "Satanic Mills," whose technology was invented

> *"To perplex youth. . .& to bind to labours Of day & night. . .that they might file and polish. . .hour after hour, laborious workmanship, Kept ignorant of the use that they might spend the days of wisdom In sorrowfull drudgery to obtain a scanty pittance of bread. In ignorance to view a small portion & think that All. And call it demonstration, blind to all the simple rules of life."*

Several people in the following century were influenced by Blake's attitudes and perceptions, but most of them wanted to retreat to a simpler past, rather than (as Blake desired) to advance into a more generous future.

"And when all Tyranny was cut off from the face of the earth living flames winged with intellect and Reason, round the Earth they march in order, flame by flame. . . .Start forth the trembling millions into flames of mental fire. . . "Why sit I here & give up all my powers to indolence. . .?

That idea, that people would "ignite mentally" when oppression disappears, has become a recurring controversy. (J.D. Unwin vs. J. Prescott, for example.) In 1961, James Higgins was discussing the historical lethargy of people in Latin America, which is usually blamed on the tropical heat or an intrinsic character trait of the people. Describing the people he had met on previous trips to Cuba, who seemed lazy, careless, and sluggish, he described the change he saw after the revolution:

"And then they began to build, sing, dance, talk, to create dreams and start realizing them the next day, to plan, laugh, enjoy, to suddenly find that once they had knocked down certain artificialities, there were no longer any reasons whatsoever for not loving and helping one another. They broke through into the open and life became possible, that is, full of possibliities, real ones."

Undoubtedly the invasion and blockade subsequently affected their energies, but for a time it was a remarkable phenomenon. J.P. Sartre described it as sleep being driven from the island along with the imperialists.

I think this "sense of possibility" is an important subject to study. Poets have led the way, but science can follow.

The "romantic" poet, Hugo von Hofmannsthal, said

"The necessary is always possible. History proceeds in just that way, that something hardly

credible is treated by a few as if it could be immediately realized."

There is a sense that the future is open, or at least that it can be opened by our mental work. The musician Keith Jarrett said,

"People expect beautiful melodies. But I already know the melodies. So does everybody else. Rather than look for more beautiful melodies, everyone's purpose should be to find blind spots."

Our present lives are usually divided between routine work and entertainment. The entertainment is supposed to enliven us, to help us recover from the deadening effects of routine work. Some people put great energy and concentration into their hobbies, because they find the activity intrinsically interesting. Such intrinsic value and interest is what should be demanded of our work. But for many people, free time is routinized too. To them, Jarrett's suggestion sounds like nothing but hard work. This is where the whole person has been affected by a certain approach to work, and work is seen as something to avoid--the idle rich seem to have found the only satisfactory life.

People like Blake, Higgins, and Marx have realized that there are different ways of being, that one is fragmented and diminished, and the other is whole, alive, and growing. When people feel that they are in possession of their own lives, then problems become opportunities. Each problem leads to new problems. The world draws us forward, and we are not defined by an "occupation" or "profession," but by the work we have achieved, and the problems we have confronted.

CHAPTER 19

THE EXPANDING EARTH

In 1959 I was assigned to teach a geography course that I wasn't prepared for, so I looked around the college's 100-year-old library for some ideas. In one old book, I saw an argument for an expanding earth, based on several types of geological evidence, including fossilized sand dunes which were supposedly too steep to have been formed under the present gravitational force. Later, when I looked at a map of the floor of the Atlantic Ocean, it seemed easy to interpret the roughly parallel ridges (which weren't known in the mid-19th century when the expanding-earth/increasing gravity idea had been proposed) as the traces of past volcanic insertions along a central crack, which had led to the separation of the Americas from Africa and Europe. Other people have continued to argue that the earth might have been much smaller in the distant past.

"Several geologists, notably Oakley Shields, have shown that not only the Atlantic margins but also those of the Pacific Ocean can be fitted together, with Australia against western South America, for example. But if the Pacific Ocean formed by the division of Australia and South America at the same time that the Atlantic formed by the division of Africa and South America, all continents must have been drifting away from each other. This, of course, is impossible unless the Earth, like the universe, has expanded within the last few hundred million years. Such expansion, in

fact, has been ably argued by the Australian geologist S. Warren Carey."[1]

Oddly, most steady-state universe theories which balance lost matter with newly created matter, tend to imagine the newly created matter as appearing only in stars or in empty space. I think there is something safely abstract and "academic" about theories which ignore the earth as a possible source of new stuff; any heat inside the earth apparently seems less threatening if it is merely the cooling embers of a cosmically remote fire.

When N. A. Kozyrev theorized that time's asymmetry might itself be a source of stellar energy, he predicted that planets would also have a steady source of internal heat in proportion to their mass, and his prediction matched the known heat of the earth, but it also predicted that Jupiter would be almost star-like in its heat emission, and that even the moon would produce some internal heat. He measured hot lunar emissions in 1960, and later space exploration confirmed several other major predictions of his. I think Kozyrev's work should at least make people recognize that even local matter is cosmic.[2]

V.I. Vernadsky, widely known as a crystallographer and biogeochemist, was able to see the cosmic, philosophical, and human implications of concrete geological things. Hannes Alfven, who argues that observable (i.e., in the laboratory) electrical forces can explain large processes, such as the development of form in galaxies, also confronts the conventional attitude which prefers to separate earthly science from cosmic science. Mendeleev, in the last century, and a few contemporary scientists, including the astronomer Thomas Gold, have believed that petroleum was formed deep in the earth by geological processes. These ideas, in giving a more creative role

to the depths of the earth, have obvious cosmological significance.

Fred Hoyle and his colleagues have done some work which parallels that of Vernadsky, and which encourages a livelier way of thinking about cosmology. They have gathered spectroscopic evidence that cosmic dust (which makes up a significant part of the mass in the universe) more closely resembles bacteria than the other materials or particles which have been suggested (E. coli were used for spectroscopic comparison).

Rather than admit that certain facts are not explainable by any present conceptions, many so-called scientists will deny that such observations were made. Others will change the rules of reason, by subjectivizing science, resorting to operationalism, or to paradoxes such as wave-particle dualism.

Instead of leading to a science-mysticism, the existence of strange and conflicting observations should stimulate people to examine their assumptions, and to think new thoughts, and to devise new experiments.

In Frederick Soddy's last book, he suggested that cosmic rays might represent atoms which had been newly formed in interstellar space, and he mentioned that the permeation of space by ionized atoms, moving at high speed, would produce an evenly distributed microwave radiation. The existence of such radiation has been used by others to argue for the Big Bang story about the origin of the universe, so it is interesting that it was first mentioned in connection with a theory of continuous creation.

Early in his career, Soddy sided with Rutherford in deciding that the energy of radium came from within the atoms, and not from the interaction of the atoms with an energetic

medium or ether. But the question of the new creation of matter, of interactions of particles in relatively empty space, has suggested to several physicists that the properties of "empty" space should be re-examined.

H. C. Dudley and others argued that a background composed of energetic neutrinos could explain many known processes as well as, or better than, present theories. Dudley argued, for example, that nuclear fission might be random only on a relatively gross scale, and that there might be microscopic domains which resonate in certain ways with the neutrino background. He argued that unsuspected simple conditions might be able to induce or "catalyze" the resonance, leading to fission or fusion under "mild" or ordinary conditions. Unknown to Dudley, an experimental physicist (Anderson) had demonstrated non-random nuclear decay in radioactive carbon when it was applied in a monomolecular layer to aluminum foil. (By chance, Anderson's and Dudley's papers--one experimental, the other theoretical--were published within a week of each other.)

Soddy's, Dudley's, and Kozyrev's intuitions about the ways in which new energy and matter appear in the universe try to combine nearly imperceptible phenomena (time, neutrinos, background radiation) with very important processes (stellar energy, nuclear energy, cosmic rays, the creation of matter). Creation is at the heart of existence, they might say, but is too often overlooked.

The idea of an expanding earth makes the intuition more immediate and concrete. S. W. Carey has surveyed the physical processes that might account for the geological facts which point toward expansion (indicating growth that is probably increasing exponentially, with a present annual increase of about 3 square kilometers of surface area), and he has

proposed his own variant of physical theory to clarify his intuition.

But beyond the geological or cosmological issues, the expanding earth is a rich metaphor. The nature of star-energy, and the origin of life can't be such remote or abstract issues if we begin to sense the earth swelling, under and around us.

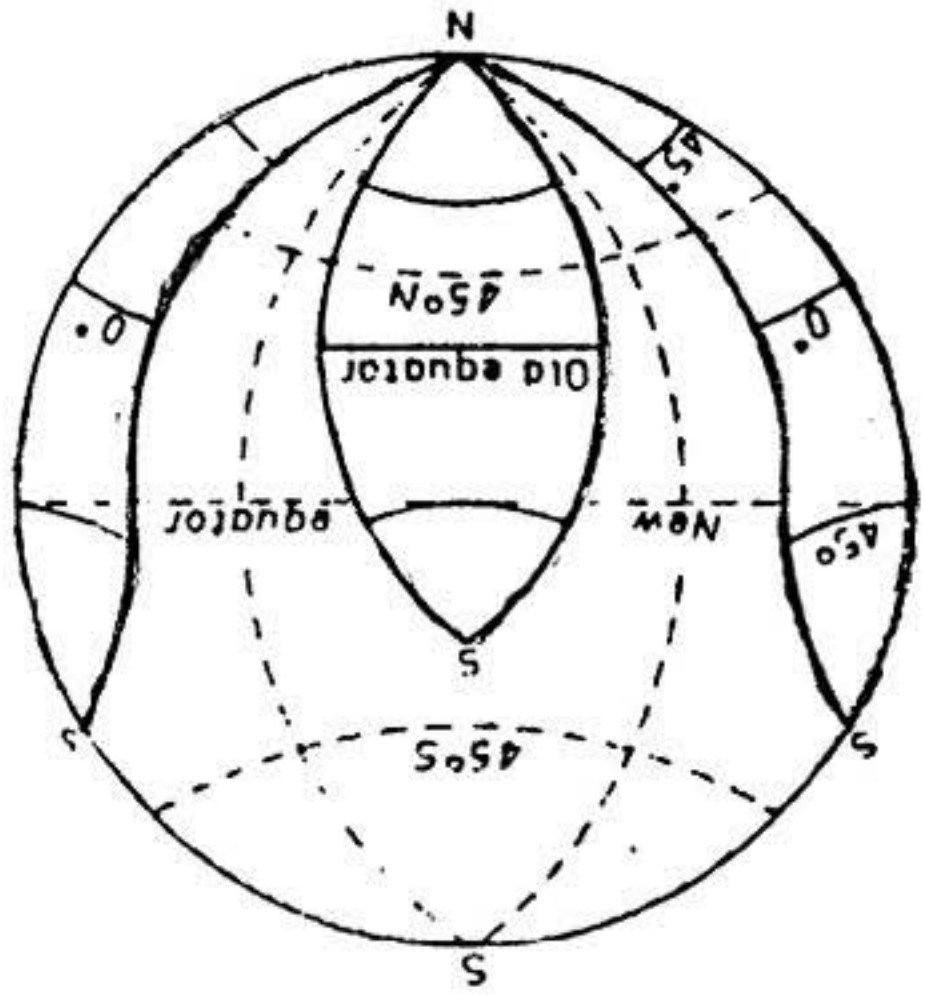
The nature of being is one boundary of the problem of understanding our own existence, and it is a moving boundary. "More, more!" is not (as Blake understood) a mistaken desire.

Another aspect of the problem of understanding has to do with our perception itself. Energized, intentional and personal, it is also responsive and public and endlessly flexible. It is part of the world, and the same motors that drive other processes must shape it. We might rephrase Le Chatelier's principle, in the way V. I. Vernadsky did, to say that systems use the energy that's available, and that our perceptions and social understandings are supported by energy flowing into the whole system. And again, there is no foreseeable limit to the intensity and richness of perception and understanding. The availability of appropriate energy--e.g., the right foods and the right fields and the right stimuli--would be the only limiting factor.

Though the "Dead Matter" theorists now dominate education, research, and medicine, and control so many other systems that the world is objectively in decline (toxins, radiation, deforestation, malnutrition, shrinking brains, extinction of species), techniques are now available to repair much of the damage and to start on an upward course. The repair and redirection begin within a system of passive constraints-- "a Mundane Shell."* The only thing that can resist the constructive organizing flow of energy is the absorptive, entropic

principle of disorganization, and as Blake pointed out, there is a limit to contraction, but no limit to expansion.

S. W. Carey's image of the earth as an opening bud is a reasonable metaphor for our present situation:



NOTE:

*Blake's phrase "Mundane Shell" refers to the confining nature of fixed opinions and beliefs in our culture.

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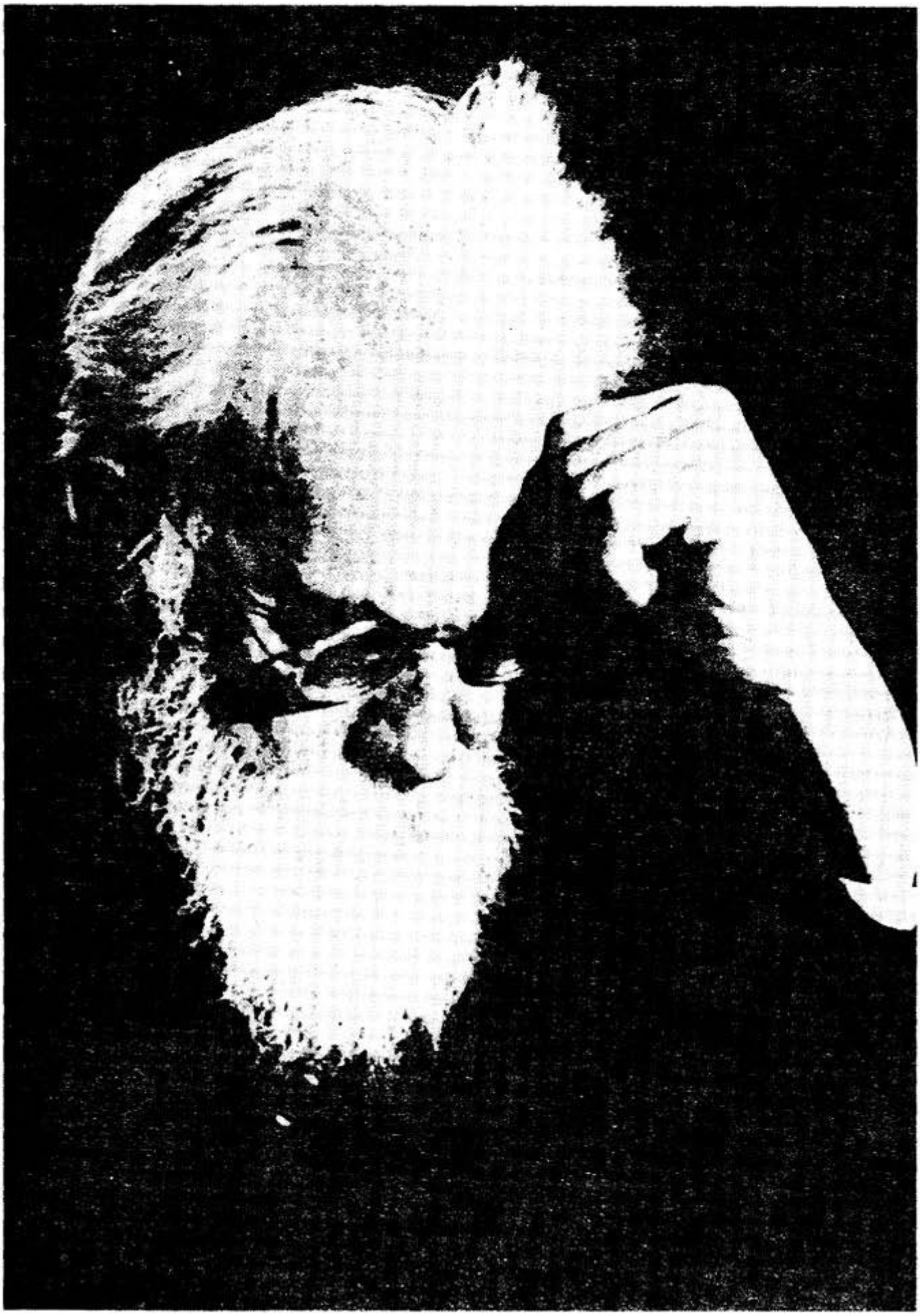
2. N. A. Kozyrev, *Possibility of Experimental Study of the Properties of Time*, JPRS: 45238, May 2, 1968.

At length for hatching ripe he breaks the shell.

One of Blake's images
of the Mundane Shell.



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Female Hormones in Context

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From PMS to Menopause: Female Hormones in Context

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Introduction

Most of the ideas about health and hormones that are being propagated are fraudulent commercial inventions. In this setting, it is impossible to have any sense of security about the way you are living unless you make the effort to critically examine the claims you hear everywhere.

Occasionally, someone complains that they "don't want to read a lot of technical stuff." (These people prefer to do what "the authorities" tell them. Where would the authorities be without them? I wouldn't want to interfere in their relationships with the authorities, except that the system they sustain is tending to kill everyone.) I have defined some of the technical words, so it shouldn't be necessary to use a dictionary too frequently. Generally, physicians have found my writing more challenging than the average woman does, because my purpose is at odds with the medical culture, and women are realizing that much of the medical culture is at odds with them.

The history of conventional medicine is mainly a history of unscientific and dangerous practices. Medical alternatives were introduced by conscientious workers to avoid the dangers of conventional medicine. But alternative approaches to medicine, especially nutritional therapies, have come to be influenced or even dominated by the same giant industries that control conventional medicine.

Many of the "preventive medicine" and "alternative health" ideas are dangerous--"estrogen replacement therapy," low protein diets, fear of milk, fear of salt, fear of shell-fish, fear of coconut oil, the avoidance of all of the best foods, emphasis on legumes and "complex carbohydrates," supplementation with fish oils and polyunsaturated seed oils, with "complete mineral supplements" (consisting of earth), with minerals "chelated" with toxins such as orotate, glutamate, and aspartate, the use of supplements containing dangerous amounts of iron and manganese, etc.

By putting the idea of eating dirt ("mined in Utah") or pond scum (various algaes) into a very limited context, the advertisers convince people that their product meets a need. Bad ideas don't look so bad, if you can write the presentation without mentioning certain drawbacks.

Good ideas are almost invariably twisted into profit-making schemes. People have come up with the idea that progesterone can be turned into a lucrative product, and--by attaching their products to the

deeply entrenched ideology of "hormone replacement therapy"--they convince people that they should keep using progesterone indefinitely, "to prevent osteoporosis." Many of these marketers advise their customers to avoid milk, and to substitute "plant proteins." (Milk actually helps to prevent and even to cure osteoporosis, because of its optimal content of calcium, protein, progesterone, thyroid, and vitamins.) Big drug companies long ago saw that progesterone wasn't appropriate for their involvement, since "a good drug is one you have to keep taking for the rest of your life."

Progesterone can relieve disabilities with great speed and safety. Since it is a protective substance that stabilizes structures and functions at many levels, it can be useful in almost any situation. It even helps the body regain its ability to produce more progesterone. But if there is a progesterone deficiency, something has caused that deficiency, and it is important to find out what the basic problem is. A diet that is deficient in high quality protein, or that contains natural food toxicants, often is responsible for a progesterone deficiency. If your diet is killing you, supplementing progesterone is of limited value.

For example, a pregnant vegetarian who has produced a long series of children with "attention deficit disorder" wants to use progesterone preventively, without changing her diet; the progesterone would undoubtedly *improve* the outcome of the pregnancy, but without an adequate diet it is certain that the outcome will not be entirely good. When such people use a "wild yam cream" during pregnancy, they are likely to blame the baby's birth defects on "progesterone," when in fact they were probably not absorbing a measurable amount of progesterone.

If progesterone is used as part of an appropriate physiological program, it isn't necessary to keep using it once it has helped to restore a balanced hormone metabolism.

This book is intended to help you preserve and promote your natural ability to produce an optimal hormonal balance. Since the greatest threat for many people is coming from the medical and nutritional industries, it is necessary to learn enough about the hormones and their physiology to be able to critically reject the impostures that are all around us. A scientific attitude is of great importance, but we must recognize that science has absolutely nothing to do with the "consensus of the authorities." You are less likely to do the wrong thing if you believe that "the authorities are always wrong," because then you will begin to question their assumptions, evaluate their evidence, and examine their reasoning.

PART ONE: ESTROGEN IN CONTEXT

1
ESTROGEN: SIMPLY DANGEROUS

The questions for this chapter came from a 3 day conference in Los Angeles in 1995.

GLOSSARY:

The **pituitary gland** sits at the base of the brain, where it receives signals from the brain, and secretes hormones that regulate the production of various other hormones and secretions.

Prolactin is a hormone secreted by the pituitary gland during pregnancy, and during stress. It promotes milk production, removes calcium from the bones, and inhibits progesterone formation.

Progesterone is the main female hormone, and is a protective hormone during pregnancy, but it is also important in men since it is a general brain regulating and protective hormone.

DHEA, known as the youth hormone, is very similar to progesterone but is present in both men and women at very high levels. It can be turned into either estrogen or testosterone.

The thymus gland is the main regulator of the immune system. Estrogen causes it to shrink, while progesterone protects it.

Estrogen is a hormone that stimulates cell division (mainly in the breast, uterus, and prostate gland, and in the pituitary gland) and is normally produced in a monthly surge at the time of ovulation and during pregnancy. Women normally have higher levels in their blood than men do.

Q: What are the harmful effects of taking estrogen?

Just naming some of estrogen's effects on the body and mind that have been described in scientific and medical publications will give you at least an indication of the possibilities:

Breast cancer, uterine cancer, ovarian cancer, fibroid tumors, pituitary tumors, lung cancer, liver cancer, bowel cancer, kidney cancer, malignant melanoma, meningioma and other brain cancers, cancers of other organs, osteoarthritis, lupus, rheumatoid arthritis, allergies, porphyria, optic neuritis, epilepsy, depression, suicide, accidents, anxiety, agoraphobia, amnesia, nerve cell damage, low blood pressure, fainting, shock, migraine, varicose veins, irregular heart beat, blood vessel spasms, intestinal spasms, inflammatory bowel disease, gall stones, gall bladder spasms, blood sugar disturbances, hypothyroidism, blood clots, strokes, heart attacks, miscarriage, birth defects, endometriosis, excess hair and loss of hair, skin discoloration, thinning of the skin, water retention and obesity.

About 50 years ago, Hans Selye (known for his discovery of the stress syndrome) gave large doses of individual steroid hormones to rats to study the range of their effects. He had previously analyzed the physiology of the stress reaction, and he observed that estrogen treatment exactly duplicated the shock phase of the stress reaction. This interferes with circulation and energy metabolism, and its physiological purpose is to cause tissue to take up water which stimulates cell division, for example in the uterus to prepare for pregnancy, and in the breasts to prepare for lactation. But none of the physiological functions of estrogen suggests that it could be beneficial in situations other than reproduction--and then only when its "shock" effect is tightly regulated by a well balanced organism--and possibly in wound healing, where its ability to stimulate cell division could be useful.

Q: You mention that estrogen can cause both excess hair and loss of hair. What do you mean?

By suppressing the thyroid and stimulating the pituitary's secretion of prolactin, estrogen can have a variety of complex effects on hair growth; usually, thinning of the hair on the head is a consequence of hypothyroidism. In both men and women, loss of hair from the scalp is associated with low thyroid, but "male pattern baldness" has been held to be produced by a male hormone; but even the male hormones can be turned into estrogen by enzymes in the skin, and experiments show that it

is estrogen which causes the hair follicle to become inactive, while an estrogen-blocker can stimulate the renewal of hair. (R. C. Smart, *et al.*, *Proc. Natl. Acad. of Sciences*, Oct. 29, 1996.)

By stimulating the adrenal glands, estrogen can increase the production of the "male" hormones that are associated with whiskers and chest hair. [E. C. Ditkoff, et al., "The impact of estrogen on adrenal androgen sensitivity and secretion in polycystic ovary syndrome," J. Clin. Endocrinol. Metab. 80(2), 603-607, 1995.] This usually happens when a progesterone deficiency is combined with an excess of estrogen, as in the polycystic ovary syndrome and sometimes at menopause. In animals, polycystic ovaries are caused by a deficiency of the thyroid hormone, and the same regulatory mechanisms seem to operate in women. The polycystic ovary syndrome is the most common endocrine disorder in women during the reproductive years, and may occur in 10% of them. [A. Dunaif, et al., eds. The Polycystic Ovary Syndrome. Cambridge, MA: Blackwell Scientific; 1992.]

Q: You mentioned that estrogen causes pituitary tumors. If the pituitary is the "master gland," isn't that very serious?

In the early 1970s, researchers at Johns Hopkins studied a group of 300 young women living in their region who had pituitary tumors. Previously, that kind of tumor was very rare, and the researchers suggested that the estrogen in the oral contraceptive was causing this epidemic. Estrogen's ability to produce this kind of tumor is now firmly established. This type of tumor secretes prolactin. Prolactin is a hormone which is known to cause osteoporosis, and which also has a role in breast abnormalities, including cancer. It can suppress the ovaries' ability to make progesterone, and it affects sweat glands and hair follicles. If the tumor is very large, its pressure on the optic nerve can cause visual disturbances.

Normally, by the age of 50, most people have an enlargement of the pituitary, and this is undoubtedly a factor in the menopause and other conditions that occur in aging. A blood test for prolactin will usually show whether a tumor is forming or not. A drug is available that will shrink the tumor and normalize the gland's function.

Q: What are some of the emotional symptoms of excess estrogen?

Estrogen excess can cause suicidal depression, or milder forms of depression and lethargy, as well as irritability, aggressiveness, anxiety, fear of public places, forgetfulness, a feeling of confusion, and a tendency to cry easily. Post-partum depression (following childbirth) is associated with high estrogen and low thyroid, and insomnia is common at that time, and during menopause. Sometimes insomnia is associated with night-time worrying.

Migraine headaches are strongly associated with high estrogen and low thyroid. The traditional view that they are caused by emotions probably came from the observation that migraines are frequently associated with the monthly hormone cycle.

According to German documents [investigated by Jean Jofen of Baruch College, reported at the Fifth World Congress of Jewish Studies in Jerusalem], the Nazis put estrogen in the food at concentration camps, to make the prisoners helpless and unable to organize resistance. They certainly weren't doing it to slow the aging process.

Q: What caused your interest in estrogen?

Between 1950 and the early 1960s I knew three women who used estrogen. One developed an extreme case of rheumatoid arthritis, which got worse with each dose of estrogen, and disappeared when she stopped using it. Another woman had a mental breakdown within an hour of her estrogen injection, and was hospitalized for six months. Her daughter began using the contraceptive pill, and died of a stroke at the age of 28. It was clear to me that estrogen had harmful effects, and that it was being promoted without adequate warnings. Magazine articles described massive testing programs in Puerto Rico and claimed that the women were healthier after using the pills, but in reality the contraceptive Enovid was approved on the basis of only 135 women who were studied for a year or more; three young test subjects died. When I went to graduate school in 1968, I began projects in brain physiology, aging, and cancer, and in each of those areas I found that estrogen was an important factor.

Q: What should I do if I want to stop the pill?

In the case of birth control pills, you can simply stop taking them, with few symptoms of withdrawal, but it is important to be alert to the possibility that your own hormone balance might not spontaneously

return to normal. Some women are unable to get pregnant after using the pill. If your normal cycles don't resume within a few months, it would be useful to have tests done for prolactin, progesterone, and thyroid, since those hormones are modified by estrogen use. And you should be aware that estrogen use increases the risk of birth defects. Since natural progesterone has been found to reduce the incidence of birth defects, it would seem reasonable to be sure that your own progesterone has returned to normal before getting pregnant.

Q: How can I tell if my natural estrogen level is too high?

Only a blood test can tell for sure whether your estrogen is higher than it should be, and it is necessary to measure your progesterone at the same time, since it is best to have five or ten times as much progesterone as estrogen. If your progesterone level is low, even an average estrogen level can cause serious symptoms, because its effects are not balanced and opposed by progesterone.

Generally, people whose temperature (measured by an oral thermometer) is below normal or whose thyroid function is low are likely to have high estrogen and low progesterone. (Low temperature stimulates the ovaries to produce excess estrogen, and retards the liver's ability to excrete it.) A deficiency of protein and B vitamins can make it impossible for your liver to excrete estrogen, leading to a chronically high estrogen level. Excess fat tissue, especially after the age of 40 when progesterone and thyroid may be low, is a major cause of chronically high estrogen levels, and therefore is associated with an increased incidence of breast and uterine cancer.

Estrogen usually causes fat to be deposited on the thighs and hips.

Q: How can I get my natural estrogen level to be lower?

Adequate protein and B vitamins are essential. Vitamin A protects some tissues, such as the breasts, against estrogen's effects, including cancer, and generally offers protection against estrogen by increasing progesterone. Several studies found that vitamin E protects against estrogen's harmful effects. A thyroid supplement can reliably lower estrogen, by increasing the liver's ability to excrete it. Unsaturated oils have a strongly estrogen-promoting action, and should be avoided. Raw carrots can help, by preventing the reabsorption of estrogen which has been secreted into the intestine with the bile. Adequate sunlight helps

to maintain a healthy balance of the hormones. In certain circumstances, natural progesterone can help to reestablish a balance of hormones.

Q: Will lowering my estrogen have any harmful effects?

No. Natural estrogen is closely associated with stress, and this "anti-estrogen" program is essentially an antistress program, which is likely to improve many aspects of your health.

Q: What are my options for birth control if I don't take estrogen?

Human fertility, like that of birds, reptiles, fish, and other animals, has declined so steeply during the last 20 years, as a result of the industrial pollutants with harmful estrogen-like effects, that it is very likely that every form of birth control has become more effective than it was found to be in the 1960s and 1970s. This means that even the rhythm method, using temperature or mucous tests to determine the fertile time, should be more effective than it used to be. The barrier methods--condoms, diaphragms, and cervical caps--will tend to be more effective even without the toxic spermicidal drugs that are now normally used with them.

The traditional cervical cap was illegal in the United States for many years. (In fact, contraception was a crime not very long ago. And when I first considered including contraception in a course I taught, I learned that even teaching about it would have been illegal. It was undoubtedly lobbying by the pharmaceutical industry that contributed to the changed legal situation.) When a so-called cervical cap was finally approved for use in this country, it was actually an unworkable, ludicrously designed receptacle for a spermicidal drug, and not actually an effective barrier. The actual cervical cap, if it can be obtained "illegally," is a safe, easy, comfortable and effective means of contraception.

The IUD (intrauterine device) actually works by causing serious hormonal disruptions, blocking the ability to produce progesterone.

Natural progesterone has been added to plastic IUDs, but this doesn't correct the general hormone imbalance that can be produced by the presence of an object in the uterus.

Synthetic hormones which are implanted under the skin increase the risk of cancer, and can cause disfiguring injury at the site of implantation.

Natural progesterone placed in the vagina during intercourse has been very effective in my studies, but is not officially approved.

Progesterone's normal effects include maintenance of pregnancy, and that requires the prevention of additional pregnancies during the course of an established one. Its presence in the vagina during intercourse causes the cells to react as if there were already an established pregnancy. There are various reasons that this method of contraception hasn't been generally accepted; for example, progesterone's very name suggests that it promotes pregnancy, and the bureaucratic mentality sees things in simplistic ways.

Incidentally, I think the evidence is absolutely clear that the estrogen pills are not contraceptives. They don't prevent conception, they prevent implantation of the embryo into the uterus. That is abortion, so the industry had to make up a theory in which the pills could be marketed as a contraceptive, to avoid the religious reaction to the abortion pill. This theoretical gimmick took nearly twenty years to develop.

SUMMARY

There is no valid scientific evidence of its safety in any amounts.

Estrogen's contraceptive action is just one aspect of its general toxic effect.

Estrogen is dangerous, in any amounts, unless it is balanced by an abundance of the natural forms of thyroid, progesterone, and DHEA.

Estrogen is a cumulative toxin, because it causes changes in every system of the body, even when present in normal amounts. These cumulative changes appear to accelerate aging in all tissues.

2
ESTROGEN: THE HOAX OF "REPLACEMENT"

GLOSSARY:

Progesterone is the main female hormone, and is a protective hormone during pregnancy, but it is also important in men since it is a general brain-regulating and protective hormone.

DHEA, known as the youth hormone, is very similar to progesterone but is present in both men and women at very high levels. It can be turned into either estrogen or testosterone.

The thymus gland is the main regulator of the immune system.

Testosterone is the main male hormone, though it is present in females too.

Free radicals are parts of molecules that can react destructively with other molecules to cause damage to cells.

HDL and **LDL** are often called "good cholesterol" (High Density Lipoproteins) and "bad cholesterol" (Low Density Lipoproteins) because of a slight association between their ratio and heart disease, but in fact the ratio that suggests freedom from heart disease suggests susceptibility to cancer. LDL ("bad") is extremely good because it is used as the source for producing progesterone and DHEA.

Q: You point out the dangers of estrogen, but don't women need to replace it at menopause?

"Replacement" is a trick word in this context. At a European conference, a researcher asked "why do you Americans use the word 'replacement,' when you are administering doses that give them 15 times more estrogen than normal young women have naturally?" Rather than bringing the blood level of estrogen up to normal, most physicians ignore the amount of estrogen already present in the blood, and give a dose of

estrogen sufficient to suppress the pituitary hormones, FSH and LH, which are sometimes called "the menopause hormones."

But the menopausal excess of those pituitary hormones is caused by estrogen's chronic damage to the nerve cells that regulate the pituitary, which causes the nerves to become insensitive to normal stimulation by estrogen.

Cholesterol is turned into hormones such as progesterone in the brain and the adrenal glands, as well as in the ovaries and testicles, but estrogen can be produced in practically every part of the body. For example, *even when the ovaries are removed*, hormones from the adrenal glands can be turned into estrogen in fat cells. In general, the fatter a person is, the higher their estrogen levels are. This is why the risk of cancer increases in proportion to obesity.

The stimulating effect some women experience when they are given large, unphysiological doses of estrogen seems to be produced partly by an effect of estrogen that resembles stimulation by cocaine. In a variety of ways, estrogen is a powerful brain excitant: it can provoke epileptic seizures, and it increases the effects of some of the excitatory substances and processes that contribute to brain aging.

Q: How safe is it for a woman to take estrogen?

It simply isn't safe to take estrogen. Safety implies that adequate studies have been performed, and have found that the treatment has done no harm. The first such large scale study to examine the general effects of estrogen replacement is just beginning. Many studies which looked for particular effects in humans have already found harm, and the huge amount of research that has been done on animals strongly indicates that the over-all effects of estrogen will be found to be harmful.

During the 20th century, animal studies have revealed almost an infinite variety of harmful effects of estrogen. Cancer, blood clots, miscarriage, shock-like effects, and accelerated aging are among its longest-established toxic effects. Some medical publications have claimed that estrogen-treated women live longer than untreated women, but as Dr. Elizabeth Barrett-Connor (UCSD) has observed, the women who received estrogen were healthier before the study began than the women who didn't receive estrogen, and in such a biased situation no meaningful conclusion is possible, except that some women can survive treatment with estrogen. There are many scientifically sound studies that show estrogen treatment to be seriously harmful to women. Even some of

estrogen's less deadly effects, such as memory impairment and water retention, should be taken more seriously.

Q: How safe is estrogen in very low doses?

It's not safe even in low doses.

"Low estrogen" birth control pills contain about 30 micrograms of estrogen, and since this amount prevents pregnancy, it is significantly "large" in physiological terms. It is low only by reference to earlier pills. Even young women have had strokes caused by the estrogen in birth control pills, and tumors of the pituitary and liver have been linked to use of the pill, as have cancer, heart disease, inflammatory bowel disease, suicides, and accidental death. Since many environmental pollutants (DDT, phenolic compounds, smoke and dioxins, for example) act like estrogen, it is increasingly difficult to distinguish the effects of medical estrogens from the general effects of pollution, but the higher background level of estrogenic stimulation suggests that more and more people will be injured by the additional burden of "low dose" estrogen treatments. (Skin patches for menopause treatment are intended to deliver 50 or 100 micrograms of the powerful natural estrogen, estradiol, per day, vaginal creams deliver similar amounts (probably causing higher blood concentrations at times, because of the greater permeability of vaginal membranes), and the suggested oral dose of estradiol for menopause symptoms is 1 or 2 mg., that is, 1000 or 2000 micrograms per day. Tablets of conjugated estrogen for oral use range from 300 micrograms to 2,500 micrograms. As a vaginal cream, the applied dosage suggested is 1,250 or 2,500 micrograms per day for the conjugated estrogen, somewhat lower than the suggested amount of estradiol cream.)

Q: Why would the medical establishment prescribe estrogen if it's not safe?

Hundreds of millions of dollars of annual profits from estrogen products allow the drug companies to subsidize medical conferences, medical research, medical journals, and medical schools. The information physicians receive is heavily biased in favor of estrogen treatment by that funding. Physicians are not regularly taught in medical school or in continuing education courses, that they should measure the amount of estrogen in the blood before they prescribe a treatment to "replace" it, and the amount commonly prescribed has no meaningful relationship to

the amount which is normal in young women. Many women have told me that their doctors have measured their estrogen level, but when they look at their medical records they often find that only the pituitary hormones or the vaginal cells have been examined.

Q: Doesn't taking estrogen prevent aging and increase energy?

Because of the claims that estrogen protects the skin against aging, investigators have tested its effects when rubbed onto guinea pigs (Pliske, 1953), or injected into rats (Hooker and Pfeiffer, 1943). It caused hair loss and thinning of skin in the rats, and in guinea pigs it caused degeneration and vacuolization of connective tissue. Animal experiments show clearly that estrogen accelerates the aging of connective tissues, and it causes the accumulation of "age pigment."

When a rat is treated with estrogen, it is likely to run 30 miles a day, because of the brain excitation it causes. Some women like this sensation of "energy," but biochemically, the stimulation isn't unlike that received from cocaine, and accordingly the estrogen-induced excitation seems to be addictive. Cocaine doesn't have some of estrogen's side effects. Estrogen tends to deprive all tissues of an adequate supply of oxygen, so the "energy" it provides isn't protective in the way that a good reserve of biological energy is, and in fact it activates brain pathways that involve potentially deadly over-excitation, which are responsible for the aging and death of brain cells.

Q: Why do so many women I know look and feel better when they take estrogen?

Cows and other animals that have been given estrogen treatments to make them put on extra weight, are fat and waterlogged, but none of their functional systems are improved. When a woman's skin is aging and slack, it becomes tighter and smoother if she gains weight, even if the weight consists of fat and retained water. But the skin itself becomes thinner, less elastic, and "older" in several structural and functional ways when it is treated with estrogen.

Estrogen, as discussed above, can act as a stimulant, and give an increased sense of energy. Estrogen can be metabolized into a form which promotes the actions of the *catecholamines*, such as adrenalin. In this form, estrogen produces toxic free radicals, which contribute to aging and cancer.

In those senses--tightening the aging skin by causing water retention and obesity, and acting as a stimulant--estrogen can make you "look better" and "feel better." But personality studies show that women who trust their physicians more than they trust themselves are the ones who are likely to use estrogen. What they say they feel tends to be what their physicians have told them they should feel.

Q: Doesn't estrogen prevent osteoporosis?

No. It is said that estrogen slows the rate of bone loss, while progesterone, thyroid, and DHEA actually shift bone metabolism into the growth phase. (Around the time of menopause, there is a steep decline in the levels of these three protective hormones.) But there are serious reasons for believing that estrogen is a factor in causing bone loss. Young women have thinner bones than men of the same age, because even at a young age estrogen is acting to inhibit bone *growth.* (Men's bones are 50% bigger.) Prolactin, a pituitary hormone which is increased by estrogen, has a powerful bone-weakening effect and it is often produced in excess around menopause. Cortisone, another bone-weakening hormone, also tends to be increased by estrogen. The thyroid hormone, which fundamentally supports the bone-building process, is inhibited by estrogen. And progesterone, which has a bone-protecting and bone-building effect, is inhibited by these estrogen-induced hormonal changes. When bone loss begins at the onset of menopause, it is progesterone (which normally keeps estrogen in balance) which has suddenly decreased, leaving estrogen undiminished and unopposed, usually for years, during which the worst symptoms of menopause occur.

In egg-laying chickens, estrogen promotes the storage of calcium, largely in the soft interior of bones, but if combined with a high calcium intake, extra estrogen can be toxic. To the extent that estrogen does increase the mineral content of bone, it seems to be in the spongy cancellous bone around the marrow, rather than in the strong cortical bone. In the complexly organized hormonal environment of pregnancy, estrogen's ability to stimulate the retention of iron and calcium fits into the whole scheme, in which the growing baby is consuming those substances. Poisoning by cyanide, or oxygen deprivation, can increase the retention of calcium by tissue, and since an immediate effect of estrogen is to decrease the oxygenation of tissue, I see estrogen's effect on calcium metabolism as analogous to its effect on iron: In stress,

organisms absorb calcium and iron. In dying cells, both calcium and iron tend to be deposited together. Estrogen has its place in normal growth and development, but the people who advocate its use as a supplement seem to have no respect for the complexity of its relation to the developing organism.

In young animals, estrogen retards the growth of cartilage. Physicians sometimes give estrogen to tall children, when their parents want their growth to stop, because it does stop bone growth.

Estrogen is not an anabolic hormone, like testosterone, which builds up bone and muscle. In fact, it strongly opposes the effects of those hormones. In the polycystic ovary syndrome, an excess of estrogen stimulates the adrenal glands to produce a large amount of the androgenic steroids, probably to balance estrogen in the way progesterone does when the ovaries are functioning properly. These anabolic/androgenic hormones apparently have some of the good effects of progesterone, such as reducing the incidence of cancer, but many women are disturbed by the increased growth of body and facial hair; facial features also tend to be masculinized. In France, progesterone lotions have been in use for several years for reversing some of these effects of the adrenal hormones, and for balancing estrogen.

Considering this sort of information, it is very unfortunate for women that the osteoporosis problem is so often seen simply as an opportunity for prescribing estrogen. In some countries, old women don't have a problem with osteoporosis. Shouldn't physicians pay more attention to emulating the factors that prevent osteoporosis, instead of thinking that it is a pharmacological problem?

Studies of both animals and humans show that estrogen contributes to a variety of inflammatory degenerative diseases, and one condition known to be aggravated by estrogen is osteoarthritis. Osteoarthritis is sometimes referred to as a matter of "wear" of the joints, but estrogen's contribution seems to be that it structurally weakens the joint tissues, after binding to estrogen-sensitive receptors. This research should be kept in mind when listening to the claims about its "protecting the bones." Other studies have implicated estrogen in other types of arthritis.

Q: What about taking estrogen to avoid Alzheimer's disease and heart attacks?

Several years ago it was noticed that estrogen treatment caused changes in the types and amounts of fat carried in the blood. Ordinarily, unexpected changes caused by drugs are treated as abnormalities, and bring the drug into question. But with estrogen, the situation is different: Recently, a reviewer noted that estrogen alters the triglyceride (simple fat) levels in the blood, but dismissed the change as "probably benign." In the case of cholesterol, the abnormality was interpreted as a virtue. Estrogen increased the ratio of HDL (high density lipoprotein--"good"--cholesterol) to LDL (low density lipoprotein--"bad"--cholesterol). In other situations, a high ratio of HDL to LDL has been found to be associated with a lower incidence of heart attacks (but a higher incidence of cancer), and this single trait has been considered alone, out of context, to allow many people to claim that estrogen "protects against heart attacks," since it shifts that indicator in the direction associated with fewer heart attacks. But estrogen also does many things that are more directly associated with heart attacks: It increases the tendency to form blood clots, and it increases the tendency of blood vessels to go into spasm during stress (synergizing with adrenalin). When men were given estrogen following a heart attack, it was found to increase--rather than decrease--the risk of another heart attack.

In the famous Framingham study, it was found that post-menopausal estrogen use increased heart attacks by 50% and increased strokes by 100%. "Estrogen's heart protective effect" is a clear example of taking one feature (the cancer-associated HDL/LDL ratio) out of context for the purposes of advertising a product. It is a good idea to read the literature that comes with estrogen prescription products, because even though it is printed by the pharmaceutical company, the law requires that some truthful warning information must be provided.

It is known that cancer (and other degenerative diseases) take a long time to develop, often more than 20 years after the crucial damage was done. Many studies have been able to find that estrogen has no harmful effect by stopping the study at an age at which no damage would be expected to show.

In 1993, a study in California found that women who took estrogen were less likely to develop Alzheimer's disease. The first study was done in a little town where I had done some lectures and consultations, and I was aware that a local doctor was giving his patients natural progesterone whenever he prescribed estrogen, and that he usually gave estrogen only when they specifically asked for it. I suspect that the

women who chose to use estrogen were (as in other studies) more affluent and healthier, and that many of them were at the same time taking natural progesterone.

Another more recent study showed that women who take estrogen are not less likely to develop Alzheimer's disease, but were more highly educated than those who don't use estrogen. Several studies have found that poorly educated people are much more likely to be diagnosed with Alzheimer's disease, because of the way the mental tests are designed and interpreted. These relationships show how it is possible to get a mistaken impression of the effects of estrogen treatment.

Since it is harder to do an accurate study of humans than of animals, we should examine the effects of estrogen on the brains of animals much more carefully before making any more claims about its "protective" effects. We should remember that it was claimed to prevent miscarriages (it actually causes them), to prevent skin aging (it accelerates it), to delay menopause (in animals, it accelerates the onset of sterility and the loss of cyclic pituitary function), and to prevent heart attacks in men (it caused them). As far as the brain is concerned, estrogen is known to "erase" memories, to induce seizures, to cause the exhaustion or death of particular types of nerve cell, and to be very toxic to the developing fetal brain, retarding its growth. The adrenalin-like derivative of estrogen which is responsible for much of its brain-stimulating action is known to produce toxic free radicals. Free radicals are considered to play an important role in the development of both Alzheimer's disease and heart disease.

Q: Do you mean estrogen might accelerate brain aging?

In animal studies, it accelerates age-related changes in every organ examined. In P. M. Wise's studies, it appeared to exhaust and kill specific brain cells that are involved in fertility. Recent studies of brain physiology show that estrogen and cortisol both promote the "excitotoxic" processes, which are increasingly believed to be implicated in the processes of brain aging and degeneration.

Since excess iron is now thought (as discussed in the chapter on iron) to contribute to cancer and heart disease, and is a factor in brain degeneration, and since iron assimilation is promoted by estrogen, I would expect there to be an intensification of the toxic effects of dietary iron supplementation by estrogen treatment. For example, both iron and estrogen can destabilize liver protein synthesis, they are both involved in

the formation of "age pigment," they both seem to facilitate epileptic seizures, and so on.

Menstruation, I suspect, is protective (by causing some iron loss), and estrogen (by promoting iron retention), harmful.

The incidence of Azheimer's disease is ***higher in women*** than in men [A. F. Jorm, 1990; W. A. Rocca, et al., 1991], osteoporosis is mainly a disease of American and European women, and men have more heart attacks when they are given estrogen. According to the Framingham study, women who use estrogen have more heart attacks and strokes than those who don't. Considering those simple facts, one has to wonder how the estrogen promoters came up with the theory that estrogen is "protective" against heart disease, Alzheimer's disease, and osteoporosis.

Q: My doctor said estrogen is safe if I take it with "progesterone" or progestin or testosterone.

Physicians often confuse the synthetic progestins with natural progesterone. The brand of medroxyprogesterone acetate called Provera is often mistakenly called progesterone. Each steroid hormone has a range of biological effects, and generally the synthetic progestins contain some very powerful estrogen-like or testosterone-like effects. Natural progesterone's effects on the uterus can be achieved to some extent by some of the synthetic hormones, but the natural substance also has a powerful and pervasive balancing effect on other hormones, and serves as the material out of which other natural hormones can be formed. The synthetic progestins lack that balancing effect, and can't be transformed biologically into any of the other natural hormones.

The synthetic progestins can protect the uterus from the carcinogenic effect of estrogen. Even testosterone's anti-estrogen action seems to protect the uterus and the breast from estrogen's effects. But the famous studies on female beagles showed that a commonly used synthetic progestin can cause breast cancer, and similar results have been seen with other synthetics. One of progesterone's most important effects is its protection of the brain's structure and function; the use of a synthetic substitute for it often causes nervous and emotional symptoms, and I think it is reasonable to be concerned that the synthetic may have harmful long-range effects on the brain that haven't been discovered yet.

Adding testosterone to estrogen treatment reduces some of the risks of estrogen treatment, and it definitely improves bone metabolism. Testosterone is a powerful sexual stimulant, and this has probably

increased the popularity of the treatment, but many women dislike the growth of whiskers that testosterone stimulates. [Estrogen itself can sometimes stimulate the growth of whiskers, by over-stimulating the adrenal glands. E. C. Ditkoff, et al., "The impact of estrogen on adrenal androgen sensitivity and secretion in polycystic ovary syndrome," J. Clin. Endocrinol. Metab. 80(2), 603-607, 1995.] Both testosterone and estrogen cause the thymus gland to shrink, with serious consequences for immunity, and they also seem to have some similar toxic effects on the brain.

If estrogen is not balanced by hormones such as progesterone, DHEA, pregnenolone, and testosterone, even a very small amount of the substance has a very large effect on the body. Even when the ovaries have been removed, the body's fat tissues can produce significant quantities of estrogen. Various stresses and injuries can cause the body to produce more estrogen. When large amounts of estrogen are given, the body is unable to produce enough of the other hormones to balance it, and these other hormones fail at an earlier age than estrogen production does. "Ovarian failure" always involves a progesterone deficiency, but it doesn't necessarily mean that there is an estrogen deficiency.

Natural progesterone is a cheap material which is effective when taken orally *dissolved* (not just packed) in oil, but many physicians are confused about it, because the FDA lists only the injectable form (which is in a toxic solvent) as the "approved" form. Natural progesterone, when not in an injectable form, doesn't *need* the FDA's approval, because it is a natural hormone which was in use before the FDA law was passed.

To be effective, it has to be fully dissolved and not visible as a white powder. This is why some studies have claimed that it is not effective, or is effective only when administered in very large doses.

Q: What about estriol and other estrogen choices, such as phytoestrogens (estrogens derived from plants such as soybeans)?

Estriol is a slightly weaker variant of the stronger natural estradiol. It is more water soluble than estradiol, so it is slightly easier to excrete in the urine. When it is used as a drug, the body can change it into the more active estradiol.

The phytoestrogens, or plant-derived estrogens, have been promoted recently as safer alternatives for therapeutic use. In the sense that these weaker estrogens can modify the actions of strong estrogens, they *might* be protective in *certain* circumstances involving excess

estrogen, but this protection is more theoretical than practical, and the harm they can do is real. Sheep farmers learned long ago that the phytoestrogens in clover can cause miscarriages, animal studies show they cause genital deformities, and recent tests are suggesting that they are, like other estrogens, carcinogenic. This is similar to the situation with Tamoxifen, which is an anti-estrogen used to treat breast cancer. It, in itself, is carcinogenic. (See my discussion of estriol and other "weak" estrogens in section 4.)

Q: Doesn't everyone have the right to decide what is best for them? What if they feel estrogen is working for them and eliminates symptoms?

That is reasonable, if you have access to the best information on the beneficial and harmful effects of the treatment. This book is to help you to decide whether you have the information you need on questions of this sort. Many people have felt that they understood a treatment, and benefitted from it, but later learned that it had seriously harmed them. For example, many people were given large doses of X-rays to treat their acne or ringworm or sinus inflammation or "enlarged thymus gland," with their physicians' assurance that it was the safe and effective and universally accepted treatment, only to discover that the treatment caused cancer or brain damage or deformity or loss of immunity. Many people, including physicians, do not realize that there is a very large and persuasive scientific literature that indicates that estrogen is neither safe nor effective for the various uses which are currently advertised.

Q: What are the pros and cons of other treatment regimes if I go off estrogen?

Many physicians prescribe clonidine patches to prevent hot flashes in women who don't want to use estrogen. Clonidine is a drug that blocks adrenalin. Since hot flashes can be caused by excess cortisone, and adrenalin triggers the release of cortisone, this procedure seems to have a logical foundation. Cortisone excess causes osteoporosis, so clonidine could protect the bones while preventing hot flashes.

Natural progesterone strengthens the bones by blocking cortisone and prolactin, it normalizes thyroid and energy metabolism and thereby helps with insomnia, it prevents the growth of excess facial hair, steadies the emotions, and sometimes even helps to control hot flashes.

Natural thyroid supplements can help to avoid weight gain, depression, and hot flashes; this will be discussed in the chapter on thyroid. The claims that thyroid contributes to osteoporosis are not true, according to the relevant human and animal studies (for example, Franklyn, 1994), and that myth was based on a few unscientific reports.

There is a drug which is sometimes more powerful than thyroid and progesterone in correcting abnormal pituitary function, and this has been used to relieve some of the symptoms of menopause, including osteoporosis.

The diet should support optimal functioning of the thyroid and other glands, as discussed in other chapters.

Q: How do I get off estrogen?

Keeping estrogen's stimulating action in mind, women who want to stop using estrogen prescribed "for menopause" usually find that they can withdraw from it by decreasing the dose gradually over a period of two or three months, while using some harmless stimulants such as tea or coffee as needed to smooth the process of withdrawal.

SUMMARY

Estrogen can cause breast cancer, heart disease, strokes, accelerated aging, and many other serious problems.

There is no valid scientific evidence of its safety in any amounts.

Estrogen is dangerous, in any amounts, unless it is balanced by an abundance of the natural forms of thyroid, progesterone, and DHEA.

Estrogen can be produced in practically every part of the body, especially in fat tissue.

Estrogen's only clearly established useful functions are to prepare for reproduction by stimulating growth of the uterus, the breasts, and the pituitary gland, and to influence behavior during reproduction. Even in these specialized functions, it

has an absolute requirement for a complex and precise balance of other hormones.

The body's normal defenses against estrogen fail with aging, causing many symptoms associated with menopause.

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3
AGING OVARIES: NOT THE EGGS

A few months ago public television ran a long program on the menopause, in which a rather glamorous woman physician said some shockingly ignorant things about the ovaries and menopause. I went to some book shops, to see what she might have been reading, or hearing in conversations.

One writer thought it would be nice to change the name of the menopause to "the pause." Another said it is too judgmental to say that the ovaries "fail" at menopause, and that they are really just maturing. Those concerns with terminological politeness remind me of Woody Allen's remark about death--that it is nature's way of telling us to slow down.

All of these current paperback books about menopause subscribe to the same doctrine about reproductive aging. Uniformity of opinion creates an environment in which publishers who want to sell a lot of books feel that they have to publish things that don't disturb the reading public. Books about menopause become books about an attitude toward menopause.

Even people who like to say that the ovaries "don't fail" at menopause describe a theory in which menopause and its consequences are the result of the disappearance of eggs from the ovary. That theory is so simple it can be described in three short sentences, none of which is true: (1) the ovary runs out of eggs; (2) ovulation produces hormones, so you can tell when ovulation stops because the ovaries stop producing hormones; (3) menstruation stops because ovulation has stopped. Those principles are surrounded by various corollaries. "Estrogen is the female hormone." "Estrogen deficiency accelerates aging." "Treatment with estrogen makes you more feminine." "Progesterone deficiency is the result of anovulatory cycles."

Many experimenters have demonstrated that old animals that have become infertile keep producing eggs. Several experimenters (e.g., R. R. Maurer and R. H. Foote,[1] 1971, "Maternal ageing and embryonic mortality in the rabbit," J. Reprod. Fert. 25, 329-341) have removed eggs from the ovaries of old animals, and transplanted the fertilized eggs into young animals, where the embryos were able to implant and develop normally.

I found that old animals had too little oxygen in their uterus to keep the embryo alive at the time it would normally be ready to implant itself in the uterus. Giving estrogen to a young animal causes a similar lack of oxygen in the uterus, and prevents implantation of the embryo.

At the time old animals would normally have become infertile, they remain fertile if they are given a supplement of vitamin E and progesterone. It is now established that aging animals, at the time they become infertile, are deficient in progesterone, but still produce estrogen. Even in young individuals, when stress occurs around the time of ovulation, interference with progesterone production will prevent implantation. If progesterone becomes deficient after the embryo has become implanted, miscarriage occurs.

Estrogen, acting alone or with insufficient progesterone, causes spasms in the spiral arteries that provide oxygen and nutrients to the endometrium. This seems to be the basis for menstruation, and is also believed to be a factor in miscarriage.

About 30 years ago, researchers began to understand that reproductive aging was not caused by the lack of eggs, and the aged uterus was able to support pregnancy if it had the right hormonal support. Interest turned to the brain cells in the hypothalamus which regulate the pituitary. G. H. Zeilmaker ("Effects of prolonged feeding of an ovulation inhibitor (Lyndiol) on ageing of the hypothalamic-ovarian axis and pituitary gland tumorigenesis in rats," J. Endocrin. 43, xxi, 1969)[2] was one of the first to suggest that ovarian hormones caused the brain to age. More recently, P.M. Wise[3,4] has clearly demonstrated that estrogen exhausts the cells which inhibit the pituitary gonadotropins, with the result that even abnormally high levels of estrogen are unable to turn off the pituitary secretion of the hormones that drive the ovary. Estrogen itself can impair the ovary's ability to produce progesterone, but the continuously high secretion of gonadotropins disturbs the ovary, the adrenals, and (according to recent observations) even the uterus.

Stress, especially when augmented by estrogen, leads to injury, exhaustion, and aging. The uterus and ovaries participate in the response to stress, but (as Zeilmaker and Wise have shown) the brain proves to be more directly involved in menopause than the ovaries or uterus. Coordination turns out to be crucial for complex processes such as ovulation, fertilization, and implantation. The destruction of the nerve cells that regulate the pituitary makes coordination impossible.

The issue of "running out of eggs" can be settled simply by demonstrating the presence of viable eggs at the time reproductive ability

has ended. In the 1940s, menopause was "explained" in terms of an estrogen deficiency, without a basis in fact, and now an "egg deficiency" is combined with the "estrogen deficiency," compounding the confusion. Facts aren't everything in science;* it is necessary to look at the context from which these ideas develop.

Two of America's most productive researchers in reproductive physiology, Edgar Allen and Herbert M. Evans, made observations that they believed showed that the germinal epithelium of the ovary goes through a cycle of cell proliferation that produces a new generation of oocytes during each menstrual cycle. It is recognized that new egg cells appear in the ovaries of adult prosimian primates, and at puberty in cats and pigs. Observations of newly developed egg cells have been reported in some other species. But the dominant view prefers to see the number of egg cells declining from birth, or earlier, with absolutely no new egg cells being formed later.

During gestation and infancy, the gonadotropins are very high. These hormones decline during childhood, during the time that the number of egg cells is so visibly declining. The high level of the gonadotropins during infancy hasn't been explained, but it is reasonable to suppose that it has something to do with the development of the ovaries, since a "developmental" function can be demonstrated for the gonadotropins in the ovaries and testes of older animals.

The number of brain cells peaks a few months before birth, just as the number of egg cells does. Many people have argued that this somehow means that brain cells are incapable of dividing after infancy, though there is no factual basis for making that argument, and in fact adult brain cells are now known to be able to divide. (That is true of heart cells, too.)

In a variety of tissues, it can be shown that the presence of mature cells inhibits the division of other cells. If part of the liver is removed, the remaining cells divide to replace the lost tissue. If the skin is cut, cells divide to help fill in the defect. If there is an adequate number of egg cells, this principle suggests that there is no need to produce more. There is a treatment for polycystic ovaries called "wedge resection." This can reduce the production of masculinizing hormones. By analogy with other tissues, it seems likely that the removal of a mass of malfunctioning tissue leads to the growth and development of new cells which function the way a new ovary would. Regeneration seems to be a capacity of every tissue, given the right environment. If the ovary were studied after such treatment, I suspect that "new eggs" would be found. (But even in the

seemingly simple process of healing a wound in the skin, there is still disagreement as to the relative contribution made by local cell division, and the invasion of the region by structural cells from elsewhere in the body. The appearance of a cell can be misleading; histology is often a matter of making educated guesses. For example, white blood cells can look like epithelial cells.)

Although the question of whether all the woman's eggs are in existence at or before birth doesn't logically have anything to do with the other question, whether there are still eggs in the ovary at menopause, there is a reason that people connect them. This has to do with the idea of a "germ line" as distinct from the "somatic cells." The eggs are "from the germ line," all the rest of the body (and much of the ovary) is a different sort of stuff. The "germ line" has the special property of immortality and it is "isolated" and independent. The body is susceptible to being modified by the environment, and is mortal. These are the traditional formulations of the idea, and the people who learn their orientation from textbooks are not necessarily conscious of how the ideas fit together. For biologists of my professors' generation, these ideas seemed to be a sacred core of biology, but with their death, maybe biology can be liberated.

August Weismann, working at the end of the last century and the beginning of the 20th century, created the basic ideology of genetics, to combat the idea of the inheritance of acquired characteristics, which had been supported by Darwin and others. He argued that the hereditary substance, or germ plasm, was derived only from preexisting germ plasm, and couldn't be formed anew, or modified by the environment. It created every part of the perishable body, by a process in which traits were segregated, so that the germ plasm contained the full complement of hereditary material, and each part of the body contained only the limited fraction needed for its characteristics. Thus, the body was inferior created material, while the germ line was the immortal creative stuff. Since the body adapts in response to the environment, it had seemed that these changes would be passed on to descendants, until Weismann's argument showed that it was only the perishable, dead-end body lacking the hereditary principle which was adapting. The germ line was somehow isolated from the body and from the environment.

Weismann's theoretical germ line became identified with the chromosomes and the genes. His theory was shown to be simply wrong, in that each type of cell in the body contains a full complement of chromosomes and genetic information. Although his facts were wrong,

his ideology became deeply embedded in the culture of genetics. To keep the idea that the "germ line" is somehow something distinct from the body required a special effort, once the chromosomes were seen to be identical in every part of the body. Weisman's whole point in his "germ line" idea was to show an absolute distinction between the body and the hereditary substance. If his ideology that had been built to deny the inheritance of acquired characteristics were to be saved, the *isolated* germ line would have to be found elsewhere than in the chromosomes.

The idea of "germ line (or *Keimbahn*) determinants" now took over, and was believed to be something in a certain spot in the egg. As the egg divided, into cells that look very much like each other, the cells which came from *that* part of the egg represented the germ line. As the embryo developed, the region that seemed to be traceable back to that part of the egg, represented the germ line. As the gonad began to grow, cells from the region representing the germ line were thought to travel over and invade the gonad, where they multiplied into vast numbers, but always remained the same isolated strain of germ cells with their "separate" history that could be traced back to the determinants in the special place in the egg. During the early days of embryonic development, these immigrant cells looked exactly like their neighbors which were somatic cell sprouts from the embryonic kidney region.

If it weren't for the ideology of absolute isolation of the hereditary substance, an embryologist might have suggested that cells or material of one part of the embryo *induced* a specialized, differentiated state in some cells that happened to be suitably located. If the cells derived from that certain part of the egg didn't carry unique genetic material--and they didn't--then what they carried with them was an incipient state of differentiation. Why the big deal about that particular history of differentiation? It was because the ideology that motivated Weismann was still active, and its purpose was to argue that only the "gene" was the creative productive source, and that the body--the "somatic cells"--was the passive product, whose adaptations meant nothing in the long run. This has been called the "central dogma" of genetics, that information flows only from the gene to the cell, and not back from the cell to the gene. That ideology forced geneticists to deny the existence of RNA viruses (including retroviruses such as the HIV-"AIDS" virus), and is still active in blocking research on the prion or scrapie virus, which is a protein. To say it bluntly, many highly respected biologists acted stupidly because they blindly believed in a false ideology.

Incidentally, this ideology was always impossible for horticulturists to accept, since they were in the habit of grafting (cloning) vegetative (somatic) parts of plants, which would then produce flowers and fruits. For them, the "germ" was often a product of the "body." Luther Burbank's work was consistently ridiculed by the academic biologists, who believed his achievements were impossible, that is, fraudulent. Many of Burbank's perceptions have been supported by recent evidence, but they couldn't be accepted by people whose ideology of the germ line/somatic distinction seemed to be contradicted by his work.

Another problem with the doctrine of the germ line was revealed when embryologists separated the embryo at a very early stage into two groups of cells, and found that each was able to grow into a complete animal. The idea of the germ line predicts that one member of the pair of twins could get the ability to reproduce while the other would be sterile. Some important ideas can survive their disproof.

It is exactly the same academic ideology of the priority of the germ line which blames the whole complex process of reproductive aging on the mechanical process of an "ovary running out of eggs." The ovary doesn't run out of eggs, and running out of eggs would have no great consequences if it did happen, because the main events in ovulation are produced by cells other than the eggs. But the ideology says that the "germ line" controls everything, and the eggs are the germ line. In other words, genes control the organism, and eggs control the woman.

After I had written the preceding paragraphs, Ian Wilmut's success in cloning a sheep from an adult's cell was announced. Those who still argued for Weismann's genetic interpretation of the germ line wiil probably stop talking about it, but generally, the "germ line" advocates will keep their doctrine (as empty as it is) by acknowledging the role of the cytoplasm in differentiation. The cytoplasm of the egg is constructed with the assistance of the surrounding cells of the ovary, so the important questions regarding the production of eggs will no longer be quite so obstructed by the ideology of the "germ line."

Another idea about aging of the ovary was that "old eggs" contained "old DNA," and so were defective. This was just a derivative of the idea that aging was a genetic phenomenon, and it appears that Wilmut's cloning experiment will make that argument extremely difficult to sustain. According to two variants of this theory ("Hayflick's limit," and "telomere depletion"), the cells of an adult had exhausted their "quota" of cell divisions, and so wouldn't be able to undergo enough

divisions to multiply into a new animal. The end of a dogma was mildly recognized by Professor Franklin Stahl's comment, "One often had reason to imagine that DNA suffered from irreversible changes during development." One could have imagined many things, if dogmas such as Weismann's hadn't obstructed biology for a century.

I think it will be instructive to consider the three steroid secreting glands--ovaries, testes, and adrenals--together, to see what they might have in common. In the testis, it is generally believed that pituitary gonadotropins regulate steroid synthesis and gametogenesis. In the ovaries, the gonadotropins also regulate the production of steroids, and--to some extent--the production of eggs, if not the whole gametogenic process. In the adrenal, ACTH governs the production of cortisol and sex steroids, and the transformation of the glomerulosa cell type into the other types, which secrete those hormones.

The outer layer of cells in the adrenals can form the other two cell types, and since stress-ACTH converts them to the other types, new ones must be formed. If the inner layers are removed, the whole adrenal cortex can regenerate from the outer layer. Obviously, if stress causes cells to multiply and differentiate, cells are disappearing from the inner layers.

When I was in graduate school, immunologists were aware that new cells were continually appearing in the thymus gland, but the gland didn't get bigger, and there was no visible trace of dying cells. At that time, it was considered a major puzzle, but gradually it came to be understood that a special kind of cell dissolution (called apoptosis) was occurring that accounted for the missing cells.

In the testes, apoptosis or cell-dissolution is always occurring, even though sperm cells are being produced and leaving the organ.

In the ovary, "waves" of egg cell degeneration are constantly taking place in young women. Radioactive labelling that has been used to argue that egg cells aren't being replaced seem to show that there is continual cell division in all the other ovarian cells. Interestingly, those researchers didn't seem to be interested in this apparent regeneration of the other parts of the ovary.

Apoptosis always seems to be part of a shaping process of the organ in which it occurs. Regeneration provides new cells, apoptosis recycles the substance of certain fraction of the tissue's cells. We are just starting to notice that various hormones inhibit or promote apoptosis, and so participate in the "shaping" of the organism. In many systems, it

seems that the need for a cell type or function calls it into existence, while idleness makes a cell susceptible to dissolution.

I have been referring to the "pituitary gonadotropins," and deliberately avoided referring to them as LH--luteinizing hormone--and FSH--follicle stimulating hormone--because their names reflect a theory of what they do. In some textbook descriptions of testicular function, for example, it has been said that LH produces testosterone, and that negative feedback from testosterone suppresses LH, while FSH governs the formation of sperms. That description is completely worthless, and probably was largely built up by analogy with their supposedly neatly divided functions in the ovary, reflected in their names. These gonadotropins participate in the development, maintenance, and functioning of the ovaries, and their effects depend on their timing, their balance with each other and with the steroids produced by the ovaries in response to their stimulation, and their actions are modified by many other factors, ovarian, nervous, pituitary, uterine, and immunological. During youth, the system functions in a coordinated way, with ovulation as a consequence. During aging, the crucial changes appear to be a decreased ability of the ovary and the brain to produce progesterone. Thyroid hormone, cholesterol, vitamin A and efficient cellular respiration are essential factors for synthesizing progesterone. Accumulated iron, unopposed estrogen, and impaired use of cholesterol and oxygen are factors known to contribute to the widespread and variable damage to the system of coordination.

Two things can cause the pituitary to secrete excessive amounts of the gonadotropins: A deficiency of the steroids, and damage to the steroid-sensing nerves that regulate the pituitary. When an ovary is moved (transplanted into the spleen) so that its hormones are destroyed before getting to the brain, there is hypersecretion of gonadotropic hormone,[5,6,7] and tumors develop in the ovary. The interpretation, that hypersecretion causes the tumors, is supported by other observations, e.g., that removal of one ovary increases the chance of developing a cancer in the other ovary[8] and that prolonged use of estrogen (known to create the conditions for later hypersecretion of gonadotropin[3,4]) increases the risk of ovarian cancer after menopause.[9]

Psychologists have noticed that naming an object according to a certain function often limits the way people will be able to use it. This happens in science. If we know one function of a substance, and name it for that function, we will find it harder to think of its other possible roles. Hans Selye argued that steroids, for example, should be named according

to their place of origin, rather than by a single aspect of their function. I think this applies even to the phrases "male hormone" and "female hormone": it's better to think of them in terms of their origin, and not to count on them to promote femininity or masculinity.

A note about "the female hormone." In the absence of the testicular or "male" hormones, animals differentiate as females. Recent evidence indicates that the mechanism by which testosterone masculinizes the brain requires that it be converted (in the brain) into estrogen. In this crucial event, estrogen is functioning as "the male hormone." Over the last 20 years, some types of experiment indicate that estrogen is necessary for the aggression-promoting effect of testosterone.

Progesterone is an anti-androgen, and blocks testosterone's effects. When testosterone is given to newborn or very young rats, it sets up a male pattern of hormone development, but if progesterone is given at the same time, that doesn't happen. Progesterone prevents the differentiation away from the basic female path into the male specialization. Later in life, a deficiency of progesterone in a woman can again lead to masculinization of some features, such as musculature and facial or body hair. When progesterone is given to men in large doses, it blocks various typically male processes, such as growth of whiskers. In the brain, it has a protective function in both sexes.

Estrogen promotes cell division, and is involved in essentially every tissue, in both males and females. If it is to be called a "female hormone," maybe it also has to be called "a male hormone." It does have to be present for breast development, though it is just one of many factors. In this instance, it is contributing to feminization. In other instances, it seems to contribute to virilization.

At menopause, estrogen excess can promote the production of androgens, in the absence of progesterone, which tends to defeminize the woman. This is often a result of stress, and sometimes is a consequence of hypothyroidism. In situations of this sort, estrogen is seen not to be a feminizing hormone; it is unable to neutralize the male hormones the body produces in response to the estrogen excess.

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* Since the 1930s, estrogen's toxic potential has become very clear. However, the estrogen industry doesn't want people to understand that estrogen is a shock hormone with pro-aging effects. Histamine mimics estrogen's effects on the uterus,

and antihistamines block estrogen's effects (Szego, 1965, Szego and Davis, 1967). Estrogen mimics the shock reaction. Stress, exercise, and toxins cause a rapid increase in estrogen. Males often have as much estrogen as females, especially when they are tired or sick. Estrogen increases the brain's susceptibility to epileptic seizures. and recent research shows that it (and cortisol) promote the effects of the "excitotoxins," which are increasingly implicated in degenerative brain diseases.

Currently, estrogen marketing emphasizes appearance and the danger of osteoporosis. Evidence occasionally turns up implicating estrogen in thinning of the skin and bones.[10]

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4
MENOPAUSE AND ITS CAUSES

When I was in graduate school at the University of Oregon, everyone in our lab was working on the problem of reproductive aging. Previously, people in the lab had established that the ovaries didn't "run out of eggs." There was never really any basis for that ridiculous belief. Many people just said it, the way they said "old eggs" (but never old sperms) were responsible for birth defects, or that "estrogen is the female hormone," a deficiency of which is the cause of menopausal infertility. (Old sperms have been implicated in some birth defects. People who are newly married, for example, were found to have children with fewer birth defects than people of the same age who had been married a long time, suggesting that more frequent intercourse involves fresher sperms.) When ovaries have been treated with x-rays to destroy their ability to ovulate, they have been found to produce more estrogen than before. Ovulation is one thing, and the production of hormones is another thing. You can't determine whether ovulation has occurred by measuring the hormones.

Knowing the large amount of work that has gone into our understanding of the age-related decline in fertility, it is disturbing to see people on television and in popular health books saying that menopause occurs when the "ovaries run out of eggs."

Around 1970, many people were saying that aging was caused by the loss of brain cells. There is a glimmer of truth in that silly idea, just as there would be in saying that "aging is caused by the death of skin cells," making the skin thinner and drier and less elastic. Both the brain and the skin are sources of steroid hormones, and it is possible that the death of skin cells and neurons is one factor in the age-related decline in the "sex steroids." An organism would be an easier thing to understand if cells just did their job for a certain period of time, and then died. A man named Hayflick has given people some publications to cite, when they want to simplify things by saying that aging occurs when cells have used up their quota of 50 divisions, but there are many more studies that clearly show that Hayflick's limit is nothing but a product of the cells' environment. The cell's environment, the signals and substances and energy it receives, is complex, but real progress is being made in understanding the things involved in the aging process. Luckily, the

infinite complexity of the environment is channeled into an understandable array of processes by the cell's systematic ways of responding.

I knew, from talking with L. C. Strong,[1] that early reproductive maturity was associated with early death; in his strains of cancer-prone mice, he showed that high estrogen was the cause of early puberty, a high cancer incidence, and a relatively short life. D. A. Snowdon, et al., showed that the occurrence of menopause at an early age in women is associated with a greater risk of death from all causes, including strokes and coronary heart disease.[2] (They saw ovarian aging as an indicator of general aging.) P. W. F. Wilson, et al., reported that postmenopausal estrogen use was associated with an increased incidence of heart disease and stroke.[3] P. M. Wise showed that estrogen accelerates aging of the central nervous system, destroying the nerves which regulate the pituitary gonadotropins, and causing ovarian failure and infertility.[4] Many other studies of particular tissues show that estrogen accelerates the rate of aging.

In my work with hamsters, I found that the infertility that developed at middle age was caused by a high rate of oxygen consumption in the uterus, causing the oxygen needed by the developing embryo to be consumed by uterine tissues, and causing suffocation of the embryo. This is the central mechanism by which the estrogen-containing contraceptives work: at any stage of pregnancy, a sufficient dose of estrogen kills the embryo.

Polvani and Nencioni,[5] among others, found that in women, the onset of menopause (the first missed period, suddenly increased bone loss, nervous symptoms such as depression, insomnia, and flushing) corresponds to the failure to produce progesterone, while estrogen is produced at normal levels. This results in a great functional excess of estrogen, because it is no longer opposed by progesterone. Typically, it takes about four years for the monthly estrogen excess to disappear. They suggested that the bone loss sets in immediately when progesterone fails because cortisol then is able to dominate, causing bone catabolism; progesterone normally protects against cortisol. Other researchers have pointed out that estrogen dominance promotes mitosis of the prolactin-secreting cells of the pituitary, and that prolactin causes osteoporosis; by age 50, most people have some degree of tumefaction of the prolactin-secreting part of the pituitary. But estrogen dominance (or progesterone deficiency) also clearly obstructs thyroid secretion, and thyroid governs the rate of bone metabolism and repair. Correcting the

thyroid and progesterone should take care of the cortisol/prolactin/osteoporosis problem.

P. M. Wise[4] has demonstrated that the "menopausal" pituitary hormones, high levels of LH and FSH, are produced because the regulatory nerves in the hypothalamus have lost their sensitivity to estrogen, not because estrogen is deficient. In fact, he showed that the nerves are desensitized precisely by their cumulative exposure to estrogen. If an animal's ovaries are removed when it is young, the regulatory nerves do not atrophy, and if ovaries are transplanted into these animals at the normally infertile age, they are fertile. But if animals are given larger doses of estrogen during youth, those nerves atrophy prematurely, and they become prematurely infertile.

The mechanism by which estrogen desensitizes and kills brain cells is now recognized as the "excitotoxic" process, in which the excitatory transmitter glutamic acid is allowed to exhaust the nerve cells. (This explains the older observations that glutamic acid, or aspartic acid, or aspartame, can cause brain damage and reproductive failure.) Cortisol also activates the excitotoxic system, in other brain cells, causing stress-induced atrophy of those cells.[6] Progesterone and pregnenolone are recognized as inhibitors of this excitotoxic process.

Besides estrogen's promotion of excitotoxic cell death, leading to the failure of the gonadotropin regulatory system, estrogen's stress-mimicking action probably tends to increase the secretion of LH, in ways that can be corrected by supplementing progesterone and thyroid. Since Selye's work, it has been known that estrogen creates the same conditions as occur in the shock phase of the stress reaction. (And shock, in a potential vicious circle, can increase the level of estrogen.[7]) It has recently been demonstrated that estrogen stimulates the adrenal glands, independently of the pituitary's ACTH. This can increase the production of adrenal androgens, leading to hirsutism, and other male traits, including anabolic effects.[8]

It was established in the 1950s that estrogen "erases" memories in well trained animals. I suppose that acute effect is related to the chronic toxicity that leads to cell death. (In the 1940s, DES was sold to prevent miscarriages, though it was already known that it caused them; then there was the argument that it slowed aging of the skin, despite the Revlon studies at the University of Pennsylvania showing that it accelerates all aspects of skin aging; lately there has been talk of promoting estrogen to improve memory.)

Estrogen's nerve-exciting action is known to lower seizure thresholds; premenstrual epilepsy is probably another acute sign of the neurotoxicity of estrogen.

When fatigue and lethargy are associated with aging, the brain stimulating action of estrogen can make a woman feel that she has more energy. (Large doses given to rats will make them run compulsively; running wheels with odometers have shown that they will run over 30 miles a day from the influence of estrogen.) Estrogen inhibits one of the enzymic routes for inactivating brain amines, and so it has more general effects on the brain than just the glutamate system. This generalized effect on brain amines is more like the effects of cocaine or amphetamine. If that is a woman's basis for wanting to use estrogen, a monoamine oxidase inhibitor would be safer.

The reason for the menopausal progesterone deficiency is a complex of stress-related causes. Free-radicals (for example, from iron in the corpus luteum) interfere with progesterone synthesis, as do prolactin, ACTH, estrogen, cortisol, carotene, and an imbalance of gonadotropins. A deficiency of thyroid, vitamin A, and LDL-cholesterol can also prevent the synthesis of progesterone. Several of the things which cause early puberty and high estrogen, also tend to work against progesterone synthesis. The effect of an intra-uterine irritant is to signal the ovary to suppress progesterone production, to prevent pregnancy while there is a problem in the uterus. The logic by which ACTH suppresses progesterone synthesis is similar, to prevent pregnancy during stress. Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

Chronic constipation, and anxiety which decreases blood circulation in the intestine, can increase the liver's exposure to endotoxin. Endotoxin (like intense physical activity) causes the estrogen concentration of the blood to rise. Diets that speed intestinal peristalsis might be expected to postpone menopause. Penicillin treatment, probably by lowering endotoxin production, is known to decrease estrogen and cortisone, while increasing progesterone. The same effect can be achieved by eating raw carrots (especially with coconut oil/olive oil

dressing) every day, to reduce the amount of bacterial toxins absorbed, and to help in the excretion of estrogen. Finally, long hours of daylight are known to increase progesterone production, and long hours of darkness are stressful. Annually, our total hours of day and night are the same regardless of latitude, but different ways of living, levels of artificial illumination, etc., have a strong influence on our hormones. In some animal experiments, prolonged exposure to light has delayed some aspects of aging.

General aging contributes to the specific changes that lead to menopause, but the animal experiments show that fertility can be prolonged to a much greater age by preventing excitotoxic exhaustion of the hypothalamic nerves. The question that still needs to be more clearly answered is, to what extent can general aging be prevented or delayed by protecting against the excitotoxins? Minimizing estrogen (and cortisone) with optimal thyroid activity, and maximizing pregnenolone and progesterone to prevent excitotoxic cell fatigue, can be done easily. A diet low in iron and unsaturated fats protects the respiratory apparatus from the damaging effects of excessive excitation, and--since pregnenolone is formed in the mitochondrion--also helps to prevent the loss of these hormones.

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5
NOT THE "FEMALE HORMONE," BUT THE SHOCK HORMONE

Estrogen, at least when it is not opposed by a very large concentration of progesterone, creates all of the conditions known to be involved in the aging process. These effects of estrogen include interference with oxidative metabolism, formation of lipofuscin (the age-pigment), retention of iron, production of free radicals and lipid peroxides, promotion of excitotoxicity and death of nerve cells, impaired learning ability, increased tendency to form blood clots and to have vascular spasms, increased autoimmunity and atrophy of the thymus, elevated prolactin, atrophy of skin, increased susceptibility to a great variety of cancers, lowered body temperature, lower serum albumin, increased tendency toward edema, and many of the features of shock. In recent years, it has been found to be responsible even for neonatal masculinization and the masculinization of the polycystic ovary syndrome. Although the pharmaceutical industry has often referred to it as "the female hormone," I don't know of any competent scientist who has ever called it that.

Since the 1930s, estrogen's toxic potential has become very clear. However, the estrogen industry doesn't want people to understand what estrogen is, because it is the source of billions of dollars per year for them. Estrogen is a shock hormone with pro-aging effects. In the 1930s and 1940s Loeb, Lipschutz, the Shutes, Selye, L.C. Strong, and others showed that it causes cancer, excessive clotting of the blood, shock, miscarriage, and tissue degeneration, but at the same time, the shills of the drug companies were promoting its use for preventing miscarriages and even for *preventing* the complications of pregnancy and toxemia it was known to *cause*.

The diuretic industry complemented the estrogen industry in its assault on pregnancy, creating a myth of pregnancy as a sodium-retention syndrome, when in fact an increased intake of salt is highly protective against the effects of excess estrogen and toxemia of pregnancy. (In hypovolemic shock, even a hypertonic salt solution is known to be therapeutic, and hypovolemia with hypoalbuminemia was clearly recognized as a feature of eclampsia). Thousands of well-meaning teachers and physicians helped to spread and perpetuate the fraudulent

ideas originating with the corrupt pharmaceutical industry. (The U.S. Dept. of Justice and FBI found fraud in connection with research on diuretics, but it didn't affect the FDA's approval.) After Tom Brewer's work (which built on R. Ross' and M. B. Strauss's 1935 work, and many other studies in the 1940s and 1950s), the FDA's continued approval of those drugs could only be characterized as malfeasance. (In 1834, J. Lever recognized that malnutrition and restricted salt intake could cause eclampsia. "Cases of puerperal convulsions," Guy's Hospital Reports vol. 1, series 2, 495-517, 1843.) By 1950, there was sufficient knowledge available for controlling this disease of estrogen-excess, but the mere concept of too much estrogen was anathema to the industry-agency conspirators. This is a disturbing issue, because even in 1996, prestigious professors of medicine (NPR's "Science Friday") are pretending that toxemia and eclampsia are mysterious.

Histamine mimics estrogen's effects on the uterus, and antihistamines block estrogen's effects (Szego, 1965, Szego and Davis, 1967). Estrogen mimics the shock reaction. Stress, exercise, and toxins cause a rapid increase in estrogen. Males often have as much estrogen as females, especially when they are tired or sick. Estrogen increases the brain's susceptibility to epileptic seizures, and recent research shows that it (and cortisol) promote the effects of the "excitotoxins," which are increasingly implicated in degenerative brain diseases.

Just after Szego's work was published, I suggested that antihistamines might be used to resist some of estrogen's toxic effects, including cancer. A few people tried the idea, with some benefit, but the basic idea of a physiological counterforce is opposed by the ideology of "specific chemotherapy," in cancer, epilepsy, arthritis, infertility, osteoporosis, immunodeficiency, Alzheimer's disease, etc.

The pooling of blood in veins, a basic feature of shock, has recently become another of estrogen's "protective" features for the circulatory system--the reasoning seems to be that reduced circulation of blood makes life easier for the circulatory system. The relevant contexts, though, are the contribution this makes to the formation of blood clots, and the quality of oxygenation of all tissues.

Besides causing stress, estrogen levels are increased by stress. For example, a male runner's estrogen is often doubled after a race. Men and women who are hospitalized for serious sickness typically have greatly increased estrogen levels. Estrogen's role in terminal illness, a vicious circle in which stress decreases the person's ability to tolerate stress, is seldom appreciated. Circulatory collapse, multi-organ failure,

intravascular coagulation (and the consequent depletion of fibrinogen, leading to internal bleeding) are so commonly seen in the people who die in hospitals that it would seem scandalous to suspect that estrogen could be a major contributing factor. The willingness to cover up estrogen's involvement in strokes was evident in a recent newspaper report in which a woman won a large financial settlement after her husband died from a series of strokes, caused by a pharmacy's mistakenly giving him "a female sex hormone." The mass media seem to have a "speak no evil about estrogen" policy.

Estrogen marketing involves manipulation of the mass media and the medical media. Currently, there is emphasis on appearance, heart disease, and the danger of osteoporosis. Undesirable evidence is simply ignored. I have never met a physician who had considered that estrogen might contribute to thinning of the skin and bones. Why are women's skeletons lighter than men's? This issue is sometimes noted in a tangential way (for example, see the discussions of osteoporosis and prolactin, and of prolactin and estrogen, in the Yearbook of Endocrinology, in the 1980s), but the relevant information is ignored by the influential media.

Estrogen's brain-toxic effects have been known since the 1950s, or earlier. Text-books in the 1960s discussed experiments in which either estrogen or insulin stopped growth of the fetus's brain, and also in the 1960s experiments were showing that progesterone fosters brain growth and intelligence. Zamenhoff's work showed that the prenatal abundance of glucose is a central factor in brain growth. Since estrogen and insulin lower blood sugar, and progesterone and thyroid sustain it, Zamenhoff's work showed that the level of glucose was a common factor in many of the previous experiments, though other factors, including blood volume and body temperature, are also important. The epidemiological evidence is clear that women with toxemia of pregnancy, which involves inadequate delivery of glucose to the fetus, have babies with subnormal intelligence. Among obstetricians, it used to be common knowledge (before insulin treatment became common) that diabetic women were likely to have intellectually precocious children. As the work of Shanklin, Hodin, and the Brewers shows, there is a large group of Americans with neurological damage resulting from their mothers' treatment during pregnancy.

While I was studying the effects of light on health, many of the women with the pre- or peri-menstrual syndrome told me that they had few symptoms during the summer months, so I began in the 1960s to examine the role of progesterone in health, because its synthesis is

promoted by long days. I saw that many of the sicknesses that mainly affect women had often been described as the consequence of an excess of estrogen. When animal experiments support the clinical reports and epidemiological evidence, as they do in the case of the "estrogen sicknesses," the goal of research becomes understanding the mechanisms involved, and discovering the safest way to avoid or to correct the problem. In the period between 1940 and 1960, thyroid, progesterone, and vitamins E and A had often been described as antiestrogenic substances, and some of this information persists in classical textbooks, in spite of the efforts of the drug industry to suppress the facts by giving their financial support to journals and symposia which exclude research which uses the concept of excess estrogen. For example, Goodman and Gilman's text on pharmacology discusses the ability of estrogen to make animals susceptible to seizures, and progesterone's opposing effect. One might suppose that the fact that *all of the "official" approved drugs for treating epilepsy are teratogens* should have been mentioned at that point, so that it would be brought to the attention of physicians that they had the option of using natural hormones to prevent seizures during pregancy, instead of making women choose between having a baby with birth defects, or having seizures during pregnancy. But that is not how the subject of epilepsy is presented to medical students.

It turns out that the meaning of "excess estrogen" has to be interpreted in relation to the balance of estrogen (and the multitude of factors which mimic estrogen's effects) with all of the antiestrogen factors. I have concentrated on thyroid, progesterone, and red light as the most important factors that protect against estrogen, and these all turn out to be protective against stress, shock, ionizing radiation, free radicals, lipid peroxidation, thymic atrophy, osteoporosis, arthritis, scleroderma, apoptotic cell death, and other problems that are involved in tissue degeneration or aging.

A Better Name is Needed

If animals grow up with female traits simply because testosterone is lacking, what can a "female hormone" be? If too much estrogen can make women grow whiskers, what should estrogen be called?

If we named hormones according to their place of origin, as Selye suggested, we could call estrogen folliculin (as Selye did, because it is produced abundantly in the ovarian follicle), or adipin, because it is

sometimes produced in fat cells. But it can be produced by many cells when they are under stress, and it seems to be normal for some to be produced in the testicle. (I have heard that stallions produce more estrogen than mares, though I haven't read the studies.)

If estrogen is produced by so many different cell types, could it be named according to its effects? Selye objected to that approach to naming hormones, because every hormone has a variety of functions. Nearly every type of tissue in the body contains the proteins that are called "estrogen receptors," though the receptors are not the only way estrogen affects cells. For example, it reacts with some common enzymes in cycles which produce free radicals.

I studied many different systems, trying to characterize estrogen's functions in a general way. In every system that I examined, estrogen seemed to "waste oxygen," resulting in a tendency for the tissue to be de-energized. Recent studies have used estrogen's ability to lower the cell's "energy charge" to study its ability to promote tumor growth: It lowers the energy charge in cells when it is stimulating their growth.

My results, in which estrogen interfered with respiration, made me think of Warburg's description of cancer metabolism. He saw cancer's "respiratory defect" as depriving it of the energy it needed to function as a useful tissue, leaving it only the primitive function of growth. I considered many ways in which estrogen might be a cancer hormone, including its promotion of the oxygen-wasting age pigment, and its stimulation of porphyrin metabolism, since some researchers had seen an association between cancer and porphyrins. At that time, it wasn't known that the breakdown of the porphyrin, heme, produced carbon monoxide.

But beyond the possibility that estrogen was deeply involved in the nature of cancer, I felt that its biological role had to do with its interference with oxidative metabolism. Selye had characterized estrogen's effect as "like the shock phase of the stress reaction." Estrogen does act in conjunction with histamine, and histamine alone tends to cause circulatory collapse by allowing fluid to leak out of blood vessels. Lack of oxygen probably relates more generally to the shock reaction than does histamine.

The reduction of cellular energy is probably estrogen's central action, and in Warburg's scheme, this would be the way to turn on cell division and growth. In the absence of oxygen, cells take up water, and when water-logged (even from being placed in a hypotonic fluid), they begin to divide.

Since some pituitary hormones (including prolactin, ACTH, and the gonadotropins) cause cell division in their "target organs," I suspect that they function much the way estrogen does, except that they have different affinities and so act on different types of cell.

The thyroid hormone is opposed to estrogen in many ways, promoting the delivery of oxygen to tissues, reducing tissue edema, etc. It is also antagonistic to some of the pituitary hormones, especially prolactin. In bones, prolactin causes osteoporosis, estrogen blocks bone forming processes as well as bone destroying processes, while thyroid increases bone turnover, activating both formation and removal. I'm not sure how far this generalization can be applied, but it seems that some hormones can be understood largely in terms of their pro-energy or anti-energy functions. Estrogen turns on a primitive type of growth by lowering cellular energy and function. Thyroid turns on cellular energy and function, and controls the rate of cell growth.

Some mysteries, such as the high levels of gonadotropins during infancy, might be explained by this principle: Their primary function is to regulate energy and growth. After prolonged stress or in old age, their hypersecretion would tend to cause tumors, or to de-energize cells further, causing atrophy.

Note: Although the so-called regulatory agencies have served the giant drug corporations well, by suppressing their competition and approving the most profitable drugs, in exchange for lucrative drug industry jobs offered to the officials* who do their jobs satisfactorily, the current trend in the US is to remove all constraints from the powerful corporations. Vice President Quail, with major family interests in the drug business, was put in charge of a commission to make it even easier for businesses to avoid the regulations, and similar favors are being done for the timber industry, the mass media, the banks, and the insurance industry.

New channels must be found to inform the public about the threats to their health. Even the "health food" industry is dominated by the giant corporations, so their publications don't present the alternative that used to exist, thirty years ago, in a few magazines like Prevention.

* The revolving-door between the agency and the industry--the delayed bribe--applies only for the well qualified officials. The basic function of allowing industry to do what it wants is also served by staffing the agency at lower levels with ridiculously unqualified people. The technical "training" given to people who lack any formal background in the field

apparently consists mainly of teaching them to scoff at evidence because it was published in a British or French or German or Japanese or Russian or Italian scientific journal, or because it hasn't been discussed recently in an American journal. And at all levels, the institutional principle is that if a drug doesn't cause cancer or Azheimer's disease within five years, then it is proven to be safe. At the highest level, when the agency is presented with clear evidence of fraud or malfeasance, the final response is that the agency doesn't handle complaints by individuals. I have been forced to believe that something more than incompetency is involved when officials refuse to say in writing things they have told me orally, and when they make misstatements in writing, or make deletions from documents provided under the Freedom of Information Act. And these are the guys that "work for us."

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6
JUST ONE PROBLEM: CLOTS

A stage magician can produce surprising illusions by directing the audience's attention to where something is not happening, or to a distracting gesture. The billion-dollar estrogen industry has learned the trick of directing the public's attention to where some plausible benefit might be expected, and of politely ignoring the areas where death and destruction are in fact being produced.

Interestingly, another billion-dollar industry--the edible oil industry--is using the same prestidigitation to profitably misinform the public. Decades ago, unsaturated oils were found to lower cholesterol. However, studies showed that adding the polyunsaturated oils to the diet didn't prevent death from heart disease, but that it did increase cancer deaths. There were also warnings that the oils could cause problems with blood clotting. There was silence from the industry, the government, and the medical profession in response to the bad news.

When evidence of an association between blood lipids and heart disease was found, the blood tests, rather than actual health, became the focus of publicity. A high ratio of HDL (High density lipoprotein) to LDL (low density lipoprotein) came to be identified with "health," because of its association with lower risk of heart disease, although it was also an indicator of a risk of death from cancer. By ignoring everything but heart disease, it could be argued that "If high HDL equals health, and estrogen and PUFA (polyunsaturated fatty acids) cause HDL to increase, then these things promote health."

Concerning estrogen, similarly twisted reasoning led to its trial in the 1960s to prevent heart attacks in men, but the experiment was stopped when the rate of heart attacks increased sharply.

Focus on the positive. Ignore the HDL-cancer association. Ignore the association of estrogen with thrombosis, embolism, stroke, edema, obesity, depression, myocardial infarction, eclampsia, epilepsy, brain damage, and immunodeficiency. Ignore the implications of thyroid suppression.

In her comedy routine, Judy Tenuto describes a most implausible situation, and then belligerently pleads: "It could happen; it could happen."

The ignorance or mendacity which allows experts to plead the importance of one possible benefit, in the face of clear evidence of a

multitude of serious dangers, defies any sort of conventional scientific response.

The recent corruption scandal involving the FDA's generic drug division might come to mind when I suggest that Tenuto's satire illuminates the attitude of the FDA (and the medical industry), but I believe the indictments are part of the prestidigitation.

Marvin Seife, who was head of the generic drug division, was indicted for perjury. The indicated intent of Congress had been to support generic drugs to break the monopoly of the biggest drug companies, but for the last six years there has been an intense campaign by the monopolies to keep generic drugs off the market, and Seife's indictment must be evaluated in this context.

Earlier, an FDA official who was too friendly toward DMSO and its developer, Dr. Jacob, was exposed for accepting a loan from the doctor. While keeping new entrepreneurs from intruding into the fabulously lucrative drug business, those little prosecutions allow the public to believe that the government is policing itself. (If your corporation could expect an additional $4,000,000,000 in profits in the next 10 years, but only if a few men would narrow the scope of their judgment, how do you suppose you could encourage those few men to go in the right direction?)

Forty five years ago the Shutes found that estrogen promotes the clotting of blood. At the same time, Knisely was studying the phenomenon of blood sludging, which occurs under many types of stress. At that time it was recognized that there is an equilibrium between clot formation and clot removal (fibrinolysis). Vitamin E and magnesium and some substances produced by the body shift the balance away from clots. Estrogen, calcium, altered water content and blood volume, and sluggish flow of blood encourage the formation of clots. Some contemporary articles acknowledge that estrogen can cause thrombophlebitis or thromboembolism and can exacerbate gallbladder and liver disease and breast cancer, but these warnings are subordinated to praising the benefits of estrogen replacement therapy. (Valery Miller, Veronica Ravnikar, and Chrystie Timmons, "ERT: Weighing the risks and benefits," *Patient Care*, 30-58, June 15, 1990.)

Some quotations from the ERT article by Miller, *et al.*, illustrate current medical attitudes:

"Although the reasons for its apparent protective effect on the heart are not fully understood, oral estrogen does decrease low-density lipoprotein cholesterol and increase high-density lipoprotein cholesterol." "Although no prospective study has yet shown that estrogen protects against cardiovascular disease, other studies show that women who use estrogen or who have ever used estrogen have a reduced risk of heart disease. **The only study that has not confirmed these results is the Framingham Heart Study,** which contained smaller numbers of older women and classified chest pain--a notoriously poor identifier of heart disease in women--as a cardiovascular end point" (p. 47).

The prospective long-term Framingham study noted above used to be highly praised as a source of reliable information on heart disease. In contrast, some of the studies that are praised in prestigious journals are wildly unscientific. For example, the heart disease in Marin County women receiving estrogen has been compared with that of women in the East Bay not getting estrogen. Marin County is a rich residential area, which is swept by ocean breezes, while across the bay there are more working class people (and working class men are known to have nearly 50% more heart disease than white collar workers), and the wind from one direction blows smoke from a concentration of industries and refineries, from another direction it carries the pollution from San Francisco's traffic, and from another direction it brings the agricultural poisons of the Salinas area.

If enough women die from strokes, pulmonary embolisms, accidents, suicide, cancer, and loss of immunity caused by estrogen excess, it is possible that some competent study will eventually show that estrogen treatment reduces the mortality from heart attacks, but this is not likely.

It is the estrogen in oral contraceptives which correlates with their effects on the clotting system. In the last 20 years there has been general agreement that increased risk of cardiovascular disease, rather than cancer or immunodeficiency or depression, is the most important concern about the effects of oral contraceptives.[1-11]

There are many ways that estrogen can contribute to a hypercoagulable state (leading to cardiovascular disease). Some of these involve altered liver function, including disturbed production or metabolism of 8 different coagulation controlling factors.[12,13] Since estrogen can stimulate endothelial proliferation (often cited as crucial in heart disease) and reduces the rate of venous flow,[14,15] it is necessary to

consider the whole complex circulatory system, and not just the clotting factors.

The thyroid and other hormones such as insulin and adrenalin are influenced by estrogen, and must be taken into account. Although I'm not sure what clinical perceptions led the Shutes to study estrogen's affect on clotting, pregnancy and lactation are notoriously associated with hypercoagulability (eclampsia and thromboembolism, for example) produced by the body's high estrogen production at those times.[16-23] The very high doses of estrogen that were once used to suppress lactation were found to produce clotting problems.[24] Postmenopausal use of estrogen causes changes in coagulability.[13,25,26]

In the mid-1970's when I pointed out that menopause resembles Cushing's syndrome,[27] I hadn't investigated that disease of cortisol-excess enough to know the full extent of the parallel: For example, hot flushes, night sweats, and insomnia, such common menopausal symptoms, are also common symptoms in Cushing's syndrome. Estrogen's tendency to increase cortisol production should be considered in connection with the brain-aging effects of both estrogen and cortisol[28,29]

Both estrogen and cortisol weaken the structural components of tissue, and the bruising which is so commonly associated with the premenstrual syndrome seems to involve the unopposed action of both of these hormones. The women who often have bruised thighs in their twenties are later susceptible to hemorrhages into the white part of the eye, and still later to bleeding into the brain, presumably because there is a hierarchy of protection against the tissue-weakening effects of those hormones, with the brain being the last to lose its resistance.

For example, the brain content of progesterone, pregnenolone and DHEA is normally 20 or 30 times higher than the serum concentration, and these hormones are protective against both estrogen and cortisone.

As far as I know, it is possible to have fragile blood vessels at the same time as an excessive tendency to clot, though when the vessels break the extent of the bleeding will be smaller in the hypercoagulable state. The observation that low cholesteral is associated with increased risk of hemorrhagic stroke[30] suggests that the age-related decline in progesterone, pregnenolone, and DHEA occurs earlier when there is a low level of the precursor substance, cholesterol.

Clotting too easily is just one of the problems that can be caused by an excess of estrogen, and I don't mean to give it too much emphasis, since I consider its toxic effects on the brain, and its acceleration of brain aging to be its worst effects--though its cancer inducing

effects on the uterus, the breast, the lung, the bowel and liver, and brain, are certainly serious. But at present, estrogen's cardiovascular toxicity is probably the aspect that people need to be reminded of.

The effects of estrogen on calcium metabolism--stimulating cells to take up an excess of calcium--have been known for a very long time, but accumulating knowledge shows that this excess calcium is a very important aspect of estrogen's contribution to blood clotting, heart necrosis, and tissue aging, especially brain aging. Magnesium, which is absorbed under the influence of thyroid hormone, is one of our basic defenses against the toxic effects of calcium.

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7
A LIST OF SIGNS AND SYMPTOMS THAT RESPOND TO PROGESTERONE THERAPY

Many people found the list of signs and symptoms in the first edition of this book either useful or interesting; at least it is an emphatic way of pointing out that progesterone has so many functions it can't be considered to be just a "reproductive hormone." Since I now understand better the biological meaning of these signs, I want to emphasize more strongly the importance of normalizing nutrition, thyroid function, light exposure, and bowel action in correcting the problems behind these signs and symptoms. It is really a kind of index of physiological disorders, and it happens that progesterone is a major tool for physiological adaptation.

Abdominal bloating
Accident proneness
Acne (cyclic)
Aggressiveness
Alcoholic or drug addiction
Allergic rhinitis
Appetite disturbance
Arthritis[1]
Asthma, especially in adolescence & menopause
Bleeding gums
Breast symptoms[2]
Bruising spontaneously
Capillary fragility
Carpal tunnel syndrome
Cold hands & feet
Colitis, regional enteritis
Conjunctival or retinal hemorrhage
Constipation, colicky pain
Depression
Diabetic vascular problems
Edema
Endometriosis, cervical dysplasia
Epilepsy, vertigo
Facial hair
Facial pallor, puffiness, darkening under the eyes
Fainting
Fatigue, lethargy
Fibroids
Fluctuations in weight
Formication (crawling sensation on the skin)
Gall bladder symptoms
Glaucoma (high eye pressure)
Goiter
Headache, eye pain, flashes of light, photophobia

Heart murmur
High blood pressure
Hypoglycemia
Hysteria (many emotional symptoms)
Infertility
Inflammatory and "fibrous" disease
Inner ear dizziness
Insomnia
Irritability
Low blood pressure
Lethargy and clumsiness
Menopause
Mittelschmerz[3]
Migraine
Nymphomania, loss of libido
Optic neuritis
Panic, weepiness, night-worry
Palpitations or paroxysmal tachycardia
Paraesthesias
Pituitary abnormalities
Porphyria
Sciatica
Skin disorders: facial pigmentation, erythema, urticaria
Stroke symptoms
Sweat glands: fewer functional
Toxemia of pregnancy.
Urinary frequency, etc.
Varicose veins, tired leg
Vascular abnormalities: flushing, capillary fragility, clotting, kidney underfunction, varicosities.

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1. Antibodies to joint material are found after even a mechanical or thermal injury to the joint; twisting cartilage makes it antigenic; autoimmune disease is probably nothing very special, and estrogen is now known to be responsible for many forms of it, including osteoarthritis. "Rheumatism" is an early sign of stress damage to joints. See H. Selye's publications on arthritis and scleroderma.
2. See *Annales d'Endocrinologie 37*, p. 309; Cancer 33, p. 1506; *Ann. N. Y. Acad. Sci.*, 1977. Progesterone deficiency predisposes to cancer.
3. Cramping at ovulation, often mistaken for appendicitis: in a 1962 study, 62% of all appendices removed from girls ages 11-20 were normal.

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8
ORIGINS OF PROGESTERONE THERAPY

By the beginning of the 20th century, the idea of extracting regulatory substances from animal tissues was coming into general acceptance in Western medicine. J. A. Lebreton, in Paris, was one of the first to argue for the therapeutic use of an extract of the corpus luteum. Around 1904, C. F. Burnam, of Baltimore, began using corpus luteum of the sow, administered orally, to treat the nervous symptoms associated with menopause or with the menstrual cycle, and also to treat functional amenorrhea, obesity, sterility, and habitual miscarriage. (1912 edition of New and Nonofficial Remedies, and J.A.M.A., Aug. 31, 1919, lix, p. 698.) By the 1920s, tablets of desiccated corpus luteum were generally available, and the daily dosage recommended (representing 6 to 18 grams of fresh tissue) contained a very substantial quantity of progesterone.

The chemical structure of pure crystalline progesterone was determined in 1934 (by Butenandt), and within 2 years many publications were reporting the beneficial effects of injections of the purified material. By 1935, animal research was confirming that the therapeutic work previously done with the crude extract had been on the right track. Although the early research showed that progesterone was very beneficial in threatened miscarriage, arthritis, infertility, cancer and functional diseases of the nervous system, interest in this generic, public-domain material faded as the pharmaceutical industry found methods for converting it into proprietary synthetic glucocorticoids, estrogens, and progestins.

Animals are generally more sensitive to progesterone than humans are, and in animals no toxic level has been found, except that in the highest doses it is anesthetic. In humans, even this effect has never been reported in the medical literature, and it is clearly anti-toxic in nature. Besides preventing acute poisoning of many kinds, it also reduces the incidence of birth defects and cancer.

Progesterone, the Protective Substance of Youth

In 1971, I discovered that vitamin E and progesterone work together to sustain efficient production and use of biological energy. (1)

In the mid-1970s, I found that progesterone is the most powerful order-preserving substance (anti-chaotropic) on the cellular level, and that this explains its range of protective actions, from anti-toxic to anti-stress. (2,3)

Around 1980, I discovered that vitamin E, with its crucial effect on the mitochondrial respiratory enzymes, is a uniquely powerful, stable, and biologically compatible solvent for progesterone.(4) Their intimate association at certain cellular sites requires mutual solubility. This property of mutual affinity extends to all biological areas, meaning that the solution of progesterone in vitamin E can be administered with exceptional efficiency by application to the skin or other membranes, or by ingestion, where normal digestive processes convert it into chylomicrons and distribute it to all tissues, allowing it to escape the tendency of the liver to convert it rapidly to an excretory form, as occurs when progesterone is administered in other forms.

Because of its profound biological compatibility, the progesterone-vitamin E solution permits otherwise impossibly high doses to be given, increasing by as much as 2,000% progesterone's already dramatic effects in a wide range of major biological problems, including epilepsy, habitual miscarriages, auto-immune diseases, and cancer of the uterus, breast, and kidney.

Some Aspects of Basic Progesterone Research

By 1945, Hans Selye had demonstrated that progesterone in itself has the full spectrum of regulatory and anti-stress functions of the adrenal steroids. A little later, Albert Szent-Gyorgyi showed that progesterone is able to regulate the heart, in a manner similar to digitalis. In the 1970s, I demonstrated that it acts similarly on vascular smooth muscle, regulating its tone and preventing venous pooling of blood, and maintaining normal filling of the heart, opposing shock. The immediate improvement in circulation can have dramatic effects, which include restoration of kidney function, elimination of fluid from the lungs, restoration of sensation in the feet, and healing of gangrenous toes. It restores normal tone to other smooth muscles, including the gall bladder, urinary bladder, intestine, sphincters, and uterus.

Progesterone's ability to regulate thresholds of cellular excitation operates in nerves, as well as in smooth and cardiac muscle. It sensitizes

nerves that regulate respiration, and has been used to treat infant apnea, sleep apnea in adults, and polycythemia vera in men.

In cases of specific progesterone deficiency in men, small doses can cure impotence. It has been used effectively to treat benign prostatic enlargement.

It normalizes fluid pressure, as in bursitis and glaucoma treatment. This effect on tissue fluid content is probably involved in its ability to improve oxygenation in emphysematous lungs, and to normalize swollen cartilage.

It restores many of the functions of aged skin, and is the normal defense against calcium loss from bones. It is one of the few essential requirements, besides nutrients, for nerve (brain) cell growth and survival. In young people of both sexes, the brain contains more progesterone than other organs do.

It is reasonable that progesterone, the dominant hormone in pregnancy, should have a full range of protective functions to protect the vulnerable organism during its intra-uterine life.

Practical Issues

A typical dose of progesterone/vitamin E, 20mg./day for 10 consecutive days, costs about $1.00 per month, at the present retail price. Pharmacists have the authority to compound drugs as they choose, just as physicians can prescribe the formulation they prefer. (And beyond that principle, is the fact natural hormones have never been legally even prescription drugs. Even potentially deadly injectable insulin is available everywhere without a prescription. The FDA acknowledged that they had erroneously been listing insulin as a prescription drug, when it wasn't. Federal law prohibits labeling a non-prescription drug as a prescription drug. When I asked for a copy of their policy discussions regarding natural hormones, they claimed the records were "old," and unavailable, then they said that those policy discussions were done elsewhere, so they couldn't get access to the record. It's a touchy subject; the Freedom of Information office claimed they couldn't find those old documents, and some related things they sent me were incomplete, with no explanation for the missing pages.)

Neither progesterone nor vitamin E has any toxicity when used orally. Under federal law, a prescription is needed for a dosage form of a drug that is potentially harmful. The very dangerous injectable insulin is always sold without need for a prescription, because something overrides the principle of danger, presumably that its use is conceived as akin to

nutrition, providing an essential natural substance to restore a natural function of the body. By analogy with insulin, the infinitely less dangerous progesterone should not require a prescription. The most useful terms for regulatory obfuscation are "Approved New Drug," and "not an approved drug." Most legal drugs under the 1938 FDA law have not been under the special category of "Approved New Drugs," but that is a subject the regulators just won't talk about. They talk about what they control, and hope people will assume they control everything.

Economic Questions and Pharmaceutical Efficacy

Because of its absorption by a natural digestive route which distributes it to all of the tissues, progesterone dissolved in vitamin E is almost 100% absorbed when taken orally. Less than 1% is absorbed from some types of suppositories, and less than 5% absorption is typical. Taken orally as a micronized powder, pharmaceutical efficiency is only slightly better.

Most of the valid human research before 1981 used intramuscular injections of progesterone dissolved in vegetable oil and benzyl alcohol. Benzyl alcohol has a high affinity for water, and in contact with the tissue fluid, it leaves the mixture, causing progesterone crystals to form, since vegetable oil is a poor solvent for progesterone. Therapeutic blood levels of progesterone can be achieved by intramuscular injections, but at the cost of leaving toxic debris at the site of injection. Benzyl alcohol is a powerful neuro-toxin, but its harm is reduced by progesterone's anti-toxic action. The cost of the injectable progesterone, and especially of the injection itself, has been the main factor preventing wider acceptance of this form of progesterone in the United States, since the solvent's toxicity has never been discussed officially.

The chemistry for converting crude diosgenin into pregnenolone, and for converting pregnenolone into progesterone, is simple enough that it can be done with little capital, at the site of production of the raw material.

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9
ANTI-AGING HORMONES: STEROIDS, IN GENERAL

This type of molecule might be the most common carbon compound in the universe. It is made by single celled organisms, by plants, and by animals, and has many kinds of function. The steroid hormones are involved in all aspects of animal physiology, and overlap with control functions of the nervous system, peptide hormones, metabolites, prostaglandins, cyclic nucleotides, etc. (I suspect that their ubiquity reflects a special kind of physical influence on biological water.) Sometimes people speak of "steroids" when they mean glucocorticoids such as cortisol or a synthetic like dexamethasone, or, among athletes, when they mean anabolic steroids or synthetic androgens; and so it is common to associate "steroids" with harmful side effects. Oddly, many people who are afraid of toxic steroids fail to realize that estrogen is a steroid, and is the most toxic steroid normally found in animals. All foods contain steroids and sterols (a major type, containing an alcohol group and a side-chain) some of which are beneficial and some of which are toxic or allergenic.

In animals, cholesterol is the basic sterol molecule, which is massively converted into other substances, including the steroid hormones. (In plants, cholesterol in very small amounts appears to serve as a hormone.) Thyroid hormone and vitamin A are required for this conversion. The first step occurs in the energy-producing mitochondrion, where cholesterol loses its side-chain and is slightly oxidized, producing pregnenolone. Being less fat soluble than cholesterol, pregnenolone leaves the mitochondrion, so it tends not to inhibit its own synthesis.

Rather, it seems to stimulate its own synthesis, though this isn't as clearly established as in the case of progesterone. Depending on the tissue, pregnenolone will be converted by enzymes in the cytoplasm into either progesterone or DHEA (dehydroepiandrosterone). The fact that progesterone (and probably pregnenolone) stimulates its own synthesis means that taking it does not suppress the body's ability to synthesize it, as happens with cortisol. Sometimes, one dose or a few doses can restore the body's ability to produce enough of its own.

Progesterone also allows the thyroid gland to secrete its hormones, especially when the thyroid function has been inhibited by

estrogen. Since the thyroid hormone is needed to produce progesterone, a supplement of either tends to normalize both thyroid and progesterone production.

Progesterone and DHEA are the precursors for the other more specialized steroid hormones, including cortisol, aldosterone (sodium-retaining hormone), estrogen, and testosterone. The formation of these other hormones is tightly regulated, so that taking the precursor will correct a deficiency of a specialized hormone, but will not create an excess. At least in the case of progesterone, an excess tends to balance or neutralize an excess of the specialized hormone, so it has been described as having anti-androgenic, anti-estrogen, anti-aldosterone, and anti-cortisol functions.

Many steroids have a protective ("catatoxic") action against a wide variety of poisons. Some of the quick effects (e.g., within 10 minutes) of progesterone and pregnenolone probably represent a catatoxic action, as well as a neutralizing or balancing of excessive estrogen or cortisol. Improved metabolic efficiency, sparing oxygen and glucose, will have a quick effect in reducing edema.

During pregnancy, very large amounts of progesterone are made. It protects and stabilizes practically all functions of both the mother and the fetus. Progesterone, glucose and the thyroid hormones powerfully influence the brain development and intelligence of the baby, probably by influencing both the number and the size of brain cells, and the quality of their functioning.

Part of progesterone's protective effect is a result of its quieting effect on cells. For example, it tends to prevent seizure activity in brain cells. During childbirth, its normal function is to act as an anesthetic. When the level of estrogen is too high, progesterone can't achieve this effect. In a non-pregnant person, it is important to determine the minimum effective dose by taking only a few drops at a time, and repeating this small dose about every 20 minutes until symptoms have been controlled. Otherwise, serious "drunkenness" can be produced, with loss of coordination, and even unconsciousness.

The only solvent for progesterone which isn't toxic and which will dissolve an effective quantity, is vitamin E. In this form, it can be absorbed through the skin or other membranes, or can be taken orally. Taken orally, it is absorbed as chylomicrons, going into the general circulation (as vitamin E does), instead of to the liver where it would be prepared for excretion. In this form, therefore, it is fully and quickly available to all tissues. It is approximately 20 times more powerful in its

action than other preparations, so it is important to use it in physiological quantities, rather than in the huge doses commonly given rectally or by injection. Ten or 20 mg. is often an effective dose, though people with low thyroid or high estrogen sometimes use 50 to 100 mg. per day. In the customary 10% solution, one drop contains about 3 mg. progesterone, and 1 ml. (1/4 tsp.) contains 100 mg. The first dose should never be more than 15 mg.

Pregnenolone, taken orally, does nothing noticeable to a healthy animal or person, but if the stress-related hormones are elevated, they return to normal when pregnenolone is taken. The brain contains much more pregnenolone, DHEA, and progesterone than do other organs or the blood, and these levels decrease progressively with age. Older people are more likely to feel an effect from pregnenolone, than are young people. A tenth of a gram is a reasonable first dose, though some people seem to need as much as 1 gram per day, possibly because of poor absorption. (The amount produced daily in a healthy young adult is roughly 30 mg.)

Normalizing the stress hormones with pregnenolone often seems to have the effect of correcting the function of the thyroid gland, probably because it is suppressed by stress. Since pregnenolone is the precursor for progesterone and DHEA (and all the other steroid hormones), it often has the same effects as progesterone or DHEA, and it has the advantage that it allows the body to produce just an optimum amount of those hormones. In very old people, or people with special enzyme deficiencies, it might be necessary to supplement all three to achieve their normal physiological concentration in the tissues.

Pregnenolone and progesterone are known to protect nerves against the damaging effects of the "excitotoxins," which activate nerve cells to the point of cumulative injury during stress and fatigue. The need for pregnenolone is probably what is described as "agitated depression," in which the person feels unable to cope with ordinary life, and when the body is unable to produce enough pregnenolone, the nervous-physiological distress leads to increased production of cortisol. The clinical depression, which so typically involves elevated cortisol production, is probably primarily a pregnenolone deficiency. The active fraction of the thyroid hormone, triiodothyronine, or liothyronine (T_3), is essential for the conversion of cholesterol to pregnenolone, as is the retinol form of vitamin A. Butyric acid is known to facilitate the entry of T_3 into the mitochondrion.

Since progesterone and pregnenolone protect against the excitotoxins which damage neurons, and estrogen and cortisol promote excitotoxic damage, it seems reasonable to see this opposition as relating to their known physiological actions. For example, estrogen damages memory, and pregnenolone restores memory in old animals. Although the excitotoxins might not be involved in other organs, I suspect that something analogous (possibly the cyclic nucleotide ratio) is involved in the opposite effects of these substances on, for example, the thymus, vascular tone, and liver function.

10
YOUTH ASSOCIATED HORMONES
PROGESTERONE

Sixty years ago, progesterone was found to be the main hormone produced by the ovaries. Since it was necessary for fertility and for maintaining a healthy pregnancy, it was called the "pro-gestational hormone," and its name sometimes leads people to think that it isn't needed when you don't want to get pregnant. In fact, it is the most protective hormone the body produces, and the large amounts that are produced during pregnancy result from the developing baby's need for protection from the stressful environment. Normally, the brain contains a very high concentration of progesterone, reflecting its protective function for that most important organ. The thymus gland, the key organ of our immune system, is also profoundly dependent on progesterone.

In experiments, progesterone was found to be the basic hormone of adaptation and of resistance to stress. The adrenal glands use it to produce their anti-stress hormones, and when there is enough progesterone, they don't have to produce the potentially harmful cortisone. In a progesterone deficiency, we produce too much cortisone, and excessive cortisone causes osteoporosis, aging of the skin, damage to brain cells, and the accumulation of fat, especially on the back and abdomen.

Experiments have shown that progesterone relieves anxiety, improves memory, protects brain cells, and even prevents epileptic seizures. It promotes respiration, and has been used to correct emphysema. In the circulatory system, it prevents bulging veins by increasing the tone of blood vessels, and improves the efficiency of the heart. It reverses many of the signs of aging in the skin, and promotes healthy bone growth. It can relieve many types of arthritis, and helps a variety of immunological problems.

If progesterone is taken dissolved in vitamin E, it is absorbed very efficiently, and distributed quickly to all of the tissues. If a woman has ovaries, progesterone helps them to produce both progesterone and estrogen as needed, and also helps to restore normal functioning of the thyroid and other glands. If her ovaries have been removed, progesterone should be taken consistently to replace the lost supply. A progesterone deficiency has often been associated with increased susceptibility to cancer, and progesterone has been used to treat some types of cancer.

It is important to emphasize that progesterone is not just the hormone of pregnancy. To use it only "to protect the uterus" would be like telling a man he doesn't need testosterone if he doesn't plan to father children, except that progesterone is of far greater and more basic significance than testosterone. While men do naturally produce progesterone, and can sometimes benefit from using it, it is not a male hormone. Some people get that impression, because some physicians recommend combining estrogen with either testosterone or progesterone, to protect against some of estrogen's side effects, but progesterone is the body's natural complement to estrogen. Used alone, progesterone often makes it unnecessary to use estrogen for hot flashes or insomnia, or other symptoms of menopause.

When dissolved in vitamin E, progesterone begins entering the blood stream almost as soon as it contacts any membrane, such as the lips, tongue, gums, or palate, but when it is swallowed, it continues to be absorbed as part of the digestive process. When taken with food, its absorption occurs at the same rate as the digestion and absorption of the food.

PREGNENOLONE

Pregnenolone, which is the raw material for producing many of the hormones of stress and adaptation, was known as early as 1934, but for several years it was considered to be an "inert" substance. A reason for this belief is that it was first tested on healthy young animals. Since these animals were already producing large amounts of pregnenolone (in the brain, adrenal glands, and gonads), additional pregnenolone had no effect.

In the 1940s, pregnenolone was tested in people who were sick or under stress, and it was found to have a **wide range** of beneficial actions, but the drug industry never had much interest in it. Its very generality made it seem unlike a drug, and its natural occurrence made it impossible to patent. Thus, many synthetic variants, each with a more specialized action and some serious side effects, came to be patented and promoted for use in treating specific conditions. The drug companies created an atmosphere in which many people felt that each disease should have a drug, and each drug, a disease. The side effects of some of those synthetic hormones were so awful that many people came to fear them. For example, synthetic varieties of "cortisone" can destroy immunity, and

can cause osteoporosis, diabetes, and rapid aging, with loss of pigment in the skin and hair, and extreme thinning of the skin.

Natural pregnenolone is present in young people of both sexes at a very high concentration, and one reason for the large amount produced in youth is that it is one of our basic defenses against the harmful side effects that an imbalance of even our natural hormones can produce. In excess, natural cortisone or estrogen can be dangerous, but when there is an abundance of pregnenolone, their side effects are prevented or minimized.

In a healthy young person or animal, taking even a large dose of pregnenolone has no hormone-like or drug-like action at all. It is unique in this way. But if the animal or person is under stress, and producing more cortisone than usual, taking pregnenolone causes the cortisone to come down to the normal level. After the age of 40 or 45, it seems that everyone lives in a state of continuous "stress," just as a normal part of aging. This coincides with the body's decreased ability to produce an abundance of pregnenolone.

When aging rats are given a supplement of pregnenolone, it immediately improves their memory and general performance. Human studies, as early as the 1940s, have also demonstrated improved performance of ordinary tasks. It is now known that pregnenolone is one of the major hormones in the brain. It is produced by certain brain cells, as well as being absorbed into the brain from the blood. It protects brain cells from injury caused by fatigue, and an adequate amount has a calming effect on the emotions, which is part of the reason that it protects us from the stress response that leads to an excessive production of cortisone. People feel a mood of resilience and an ability to confront challenges.

Many people have noticed that pregnenolone has a "face-lifting" action. This effect seems to be produced by improved circulation to the skin, and by an actual contraction of some muscle-like cells in the skin. A similar effect can improve joint mobility in arthritis, tissue elasticity in the lungs, and even eyesight. Many studies have shown it to be protective of "fibrous tissues" in general, and in this connection it was proven to prevent the tumors that can be caused by estrogen.

Pregnenolone is largely converted into two other "youth-associated" protective hormones, progesterone and DHEA. At the age of 30, both men and women produce roughly 30 to 50 mg. of pregnenolone daily. When taken orally, even in the powdered form, it is absorbed fairly well. One dose of approximately 300 mg (the size of an aspirin tablet) keeps acting for about a week, as absorption continues

along the intestine, and as it is "recycled" in the body. Part of this long lasting effect is because it improves the body's ability to produce its own pregnenolone. It tends to improve function of the thyroid and other glands, and this "normalizing" effect on the other glands helps to account for its wide range of beneficial effects.

DHEA: ANOTHER YOUTH-ASSOCIATED HORMONE

DHEA (dehydroepiandrosterone) has a technical-sounding name because it has never been identified with a single dominant function, in spite of its abundance in the body. Many researchers still think of it as a substance produced by the adrenal glands, but experiments show that animals without adrenals are able to produce it in normal amounts. Much of it is formed in the brain (from pregnenolone), but it is probably produced in other organs, including the skin. The brain contains a much higher concentration of DHEA than the blood does.

In old age, we produce only about 5% as much as we do in youth. This is about the same decrease that occurs with progesterone and pregnenolone. The other hormones (for example, cortisone) do not decrease so much; as a result, our balance shifts continually during aging toward dominance by hormones such as cortisone, which use up more and more body substance, without rebuilding it. Protection against the toxic actions of these specialized hormones is a major function of DHEA and the other youth-associated hormones.

For example, starvation, aging, and stress cause the skin to become thin and fragile. An excess of cortisone--whether it is from medical treatment, or from stress, aging, or malnutrition--does the same thing. Material from the skin is dissolved to provide nutrition for the more essential organs. Other organs, such as the muscles and bones, dissolve more slowly, but just as destructively, under the continued influence of cortisone. DHEA blocks these destructive effects of cortisone, and actively restores the normal growth and repair processes to those organs, strengthening the skin and bones and other organs. Stimulation of bone-growth by DHEA has been demonstrated *in vitro* (in laboratory tests), and it has been used to relieve many symptoms caused by osteoporosis and arthritis, even when applied topically in an oily solution.

Estrogen is known to produce a great variety of immunological defects, and DHEA, apparently by its balancing and restorative actions, is

able to correct some of those immunological defects, including some "autoimmune" diseases.

It is established that DHEA protects against cancer, but it isn't yet understood how it does this. It appears to protect against the toxic cancer-producing effects of excess estrogen, but its anti-cancer properties probably involve many other functions.

Diabetes can be produced experimentally by certain poisons which kill the insulin-producing cells in the pancreas. Rabbits were experimentally made diabetic, and when treated with DHEA their diabetes was cured. It was found that the insulin-producing cells had regenerated. Many people with diabetes have used brewer's yeast and DHEA to improve their sugar metabolism. In diabetes, very little sugar enters the cells, so fatigue is a problem. DHEA stimulates cells to absorb sugar and to burn it, so it increases our general energy level and helps to prevent obesity.

Young people produce about 12 to 15 milligrams of DHEA per day, and that amount decreases by about 2 mg. per day for every decade after the age of 30. This is one of the reasons that young people eat more without getting fat, and tolerate cold weather better: DHEA, like the thyroid hormone, increases our heat production and ability to burn calories. At the age of 50, about 4 mg. of DHEA per day will usually restore the level of DHEA in the blood to a youthful level. It is important to avoid taking more than needed, since some people (especially if they are deficient in progesterone, pregnenolone, or thyroid) can turn the excess into estrogen or testosterone, and large amounts of those sex hormones can disturb the function of the thymus gland and the liver.

11
THYROID

Measuring the amount of thyroid in the blood isn't a good way to evaluate adequacy of thyroid function, since the response of tissues to the hormone can be suppressed (for example, by unsaturated fats).

In the 1930s accurate diagnosis was made by evaluating a variety of indications, including basal oxygen consumption, serum cholesterol level, pulse rate, temperature, carotenemia, bowel function, and quality of hair and skin. A good estimate can be made using only the temperature and pulse rate. (Pulse rate should be thought of as an indicator of the rate of blood circulation, meaning that the strength of the pulse should increase with the rate; a rapid but weak, shock-like pulse gives useful information, but has a different meaning.)

Oral or armpit temperature, in the morning before getting out of bed, should be around 98 degrees F, and it should rise to 98.6° by mid-morning. This is not valid if you sleep under an electric blanket, or if the weather is hot and humid. A person who is hypothyroid produces heat at a low rate, but doesn't lose it at the normal rate, since there is less sweating, and the skin is relatively cool. Many hypothyroid people compensate with high adrenalin production (sometimes 40 times higher than normal), and this tends to keep the skin cool, especially on the hands, feet, and nose. The high adrenalin is the consequence of low blood glucose, so a feeding of carbohydrate, such as a glass of orange juice, will sometimes lower the pulse rate momentarily. Since thyroid is essential for producing progesterone, and progesterone is "thermogenic" in the sense of setting the temperature control system higher, the body sometimes maintains a subnormal temperature even in warm weather, Healthy populations have an average resting pulse rate of about 85 per minute. Especially in hot weather it is useful to consider both temperature and pulse rate.

The Achilles tendon reflex is another quick way to estimate thyroid function. This reflex is used because of the insignificant weight of the toes in relation to contraction of the gastrocnemius muscle. The T (repolarization) wave on the electrocardiogram is a similar indicator of the rate of energy production. Thumping the Achilles tendon causes the muscle to contract (unless it is already in a semi-contracted state, which isn't uncommon). The contraction consumes energy, and the muscle can't relax until enough energy has been produced to restore the threshold and

the readiness for a new contraction. (Creatinine levels are a vague indicator of the activity of this system, and are often a little low in hypothyroidism.)

If energy production is efficient, relaxation is faster than the passive return motion of the foot, so the foot swings freely back to its original position, and over-shoots slightly, causing a slight swinging action. In hypo- thyroidism, the foot returns as if controlled by a pneumatic door-closer, and settles slowly and precisely into its relaxed position, sometimes with a hesitating, intermittent motion. This slow replenishment of energy, and slow relaxation, can cause muscles to cramp easily. The aching leg muscles of children at the end of an active day are often a sign of hypothyroidism, and sometimes the gastrocnemius muscle become very swollen and hypertrophied in hypothyroid children. The same process, of slow energy regeneration, can cause rhythm disturbance in the heart, and often causes insomnia and restless sleep.

The thyroid gland secretes about 3 parts of thyroxin to one part of triiodothyronine, and this allows the liver to regulate thyroid function, by converting more of the T_4 to the active T_3 when there is an abundance of energy. Glucose is essential for the conversion, so during fasting there is a sharp decrease in metabolic rate, and in experiments, 200 or 300 calories of carbohydrates can be added to the diet without causing fat storage.

When the liver is the main cause of hypothyroidism, your temperature (and especially the temperature of your nose, hands and feet) will fall when you are hungry, and will rise when you eat carbohydrates. If a hypothyroid person has a very slow pulse, and feels lethargic, it seems that there is little adrenalin; in this case, a feeding of carbohydrate is likely to increase both the pulse rate and the temperature, as the liver is permitted to form the active T_3 hormone.

Women often have above-average thyroxin, with symptoms of hypothyroidism. This is apparently because it isn't being converted to the active form (T_3). Before using a Cytomel (T_3) supplement, it might be possible to solve the problem with diet alone. A piece of fruit or a glass of juice or milk between meals, and adequate animal protein (or potato protein) in the diet is sometimes enough to allow the liver to produce the hormone. If Cytomel is used, it is efficient to approximate the physiological rate of T_3 formation, by nibbling one (10 or 15 mcg.) tablet during the day. When a large amount is taken at one time, the liver is likely to convert much of it to the inactive reverse-T_3 form, in a normal defensive response.

Women normally have less active livers than men do. Estrogen can have a directly toxic effect on the liver, but the normal reason for the difference is probably that temperature and thyroid function strongly influence the liver, and are generally lower in women than in men. Estrogen inhibits the secretion of hormone by the thyroid gland itself, probably by inhibiting the proteolytic enzyme which dissolves the colloid. Progesterone has the opposite effect, promoting the release of the hormones from the gland. At puberty, in pregnancy, and at menopause, the thyroid gland often enlarges, probably as a result of estrogen dominance.

Thyroid function stimulates the liver to inactivate estrogen for secretion, so estrogen dominance can create a vicious circle, in which excess estrogen (or deficient progesterone) blocks thyroid secretion, causing the liver to allow estrogen to accumulate to even higher levels. Progesterone (even one dose, in some cases) can break the cycle. However, if the gland is very big, the person can experience a few months of hyperthyroidism, as the gland returns to normal. It is better to allow the enlarged gland to shrink more slowly by using a thyroid supplement. If an enlarged gland does begin to secrete too much thyroid hormone, it can be controlled with tablets of propylthiouracil, or even with raw cabbage or cabbage juice, and cysteine-rich meats, including liver.

Besides fasting, or chronic protein deficiency, the common causes of hypothyroidism are excessive stress or "aerobic" (i.e., anaerobic) exercise, and diets containing beans, lentils, nuts, unsaturated fats (including carotene), and undercooked broccoli, cauliflower, cabbage, or mustard greens. Many health conscious people become hypothyroid with a synergistic program of undercooked vegetables, legumes instead of animal proteins, oils instead of butter, carotene instead of vitamin A, and breathless exercise instead of a stimulating life.

A good diet, plus a supplement of either thyroid or progesterone, can often break the cycle of hormonal imbalance.

If a person has at least a normal level of cholesterol, it is very likely that a progesterone deficiency can be corrected by normalizing the thyroid function, since thyroid, vitamin A, and cholesterol are the main factors in the synthesis of progesterone. If the problem is that the ratio of estrogen to progesterone is too high, though progesterone might itself be at a reasonable level, thyroid becomes crucial, to bring the estrogen level down to normal. In hypothyroidism there is a tendency to develop cystic ovaries, and low thyroid function normally leads to estrogen dominance, even if the ovaries seem normal.

12
PROGESTERONE'S BIOLOGICAL GENERALITY

1. Intrinsic general properties.

All of the steroid functions, except those of estrogen and testosterone, are included, though weakly, in the progesterone molecule itself. These include lysosome stabilization, salt regulation, blood sugar elevation, and anesthesia (or, in physiological amounts, modulation of nerve functions). It is unusual among the steroids in promoting enlargement, rather than atrophy, of the thymus gland. Progesterone, like testosterone is anti-estrogenic.

A weak hormone activity in the absence of the stronger hormone will act as a substitute, but in the presence of the stronger hormone will weaken the strong hormone's effect by competition or "dilution" at the point of action, and possibly by suppressing the trophic pituitary agent which regulates synthesis. By thus opposing both deficiencies and excesses, such a hormone will tend to protect against pathological extremes. There is, for example, supposed to be competition between progesterone and aldosterone for the "aldosterone receptors" which cause water retention by the kidneys, so that in many situations, progesterone will relieve edema; but when the adrenal cortex is removed or fails to function (as in Addison's disease), progesterone will promote relatively normal retention of sodium and water, keeping the individual alive as long as large doses are given regularly.

Some hormones which are both progestins and anti-testosterones seem to work both at the tissue "receptor" level, and at the pituitary level. Though progesterone itself will suppress menopausal pituitary gonadotrophins, and (my observations) reduces excessive facial hair, it has not been found to have anti-testosterone effects in men when used in low doses, and in appropriate doses it can improve sexual functions in some impotent men who are deficient in progesterone. Pregnenolone (produced from cholesterol in the mitochondria), which is the precursor to progesterone and other steroids, has been used successfully to restore fertility (sperm count and motility, and, according to the wives--libido) in men.

All of the natural steroids have functions that overlap to some extent--e.g., testosterone has some progestational function--but progesterone's generality is the most remarkable.

2. Steroid precursor function.

The second aspect of progesterone's biological generality, besides its intrinsic hormonal activity, is its role as precursor for all of the other steroid hormones (see chart). When consumed in food (e.g., butter, brains, milk, ovaries--some cultures eat pork ovaries, many eat sea-urchin ovaries), it, like cholesterol, only more efficiently, enters the cycle of steroid synthesis near the beginning, so that it is a raw material, allowing normal amounts of the other hormones to be produced. This aspect of progesterone distinguishes it most strongly from the other progestins (e.g., medroxyprogesterone), which have had atoms introduced at unusual positions to inhibit metabolism and prolong activity (as well as to create a patentable and thus highly profitable substance). When we eat protein, we support the production of all the peptide hormones; likewise, natural progesterone (and pregnenolone, which is also found in brains, endocrine glands, and probably skin) serves to allow the body to produce an appropriate and balanced amount of all the other steroid hormones.

3. Anti-estrogen functions.

A third aspect of progesterone's generality is a little less clear than its intrinsic generality and its function as a general steroid precursor, because this third form has to do with its overall antagonism to estrogen, and gains significance only to the extent that we see estrogen as having a very broad physiological role--for males as well as for females. I will just mention some of the many effects of estrogen, and some reasons for its ubiquity.

Estrogen causes water retention, even when dietary salt is restricted; hyposmotic blood has been observed under estrogen influence.
Estrogen causes "erasure" of memory, as does prolactin, which is formed under the influence of estrogen.
Estrogen promotes the formation of prolactin, which normally increases with aging and stress, and which is a known contributor to osteoporosis.

Estrogen causes hypoxia at many levels--pulmonary diffusion, intracellular metabolism, and various points between.
Estrogen synergizes with insulin, lowering blood sugar, promoting fat synthesis.
Estrogen opposes actions of thyroxin, elevates the bound proportion, and blocks its secretion from the gland.
Estrogen causes reproductive aging, by exhausting neurons which regulate the pituitary.
Estrogen contributes to the risk of miscarriage and infertility.
Estrogen retards prenatal brain growth.
Estrogen promotes histamine release.
Estrogen shifts the balance of prostaglandins and cyclic nucleotides, important cellular regulators.
Estrogen and its metabolites are carcinogenic, in every sense of the word.
Estrogen promotes development of fibroids and many other kinds of tumor, including pituitary prolactin-secreting tumor.
Estrogen promotes blood clotting and increases embolism incidence.
Estrogen synergizes with adrenaline in causing vascular spasm.
Estrogen alters blood lipids and promotes gall bladder disease.
Estrogen accelerates the aging of collagen.
Estrogen mimics the shock phase of the stress reaction.
Estrogen is produced by many tissues--possibly by every tissue under certain circumstances. Stress hormones promote liver synthesis of estrogen.
Estrogen lowers the seizure threshold of nerve cells, increasing susceptibility to epileptic convulsions.
Estrogen shrinks the thymus, and contributes to many auto-immune conditions and tissue alterations including osteoarthritis.
Men and women, especially as they age, are susceptible to liver damage from toxins which can cause elevated estrogen levels by interfering with metabolism and excretion.
Malnutrition can cause signs of high estrogen.
Various physical factors, including ionizing radiation, mimic estrogen actions.
Many environmental pollutants--phenolic compounds, dioxins, PCBs, polycyclic hydrocarbons, chlorinated hydrocarbons, DDT, etc.--are estrogenic.
Estrogen promotes the retention of iron, which accumulates with aging and promotes the free-radical damage caused by stress.

In relating progesterone's effects to those of estrogen, we should avoid being misled by the opinions expressed in many textbooks, describing symptoms of the luteal phase of the menstrual cycle as symptoms "caused by progesterone." For example, many medical books promote the erroneous idea that progesterone causes edema, because edema often occurs during the luteal phase of the cycle, which is too often conceptualized as "the progesterone dominance phase." Actually, this is the time when the estrogen/progesterone ratio frequently reaches its pathological height, for four common reasons:

1. failure to eliminate estrogen;
2. failure to produce enough progesterone;
3. overproduction of estrogen;
4. excessive metabolism of progesterone.

Failure of the liver to metabolize or detoxify estrogen is equivalent to the older idea of an "elevated kidney threshold for estrogen," which was proposed as the cause of the "pre-menstrual syndrome."[1] Probably the main reason for liver sluggishness (apart from the direct action of estrogen itself, discussed in liver monographs, and often noticed in the post-ovulatory increase of susceptibility to intoxication by alcohol or other chemicals) is low thyroid, which itself is related to estrogen--about five times more women have thyroid abnormalities than men. Protein deficiency has been shown to cause the liver to fail to detoxify estrogen.[2]

Thyroid therapy normally increases assimilation of nutrients and stimulates synthesis of steroids though it lowers estrogen by promoting its metabolism in the liver. However, it increases metabolic activity systemically and can exacerbate a nutritional deficiency or a failure of steroidogenic tissue, so thyroid therapy should always be accompanied by nutritional optimization, and sometimes should be used with a steroid, preferably progesterone, to promote adrenal and other glandular function. Thyroid hormone is one of the essential factors for the conversion of cholesterol to progesterone. Progesterone promotes its own synthesis, and provides stability during adaptation.

Failure of the corpus luteum to produce adequate quantities of progesterone has been observed under various circumstances. A lack of vitamin A, and reduced circulation resulting from the prostaglandin F_2 (resulting from estrogen action, or from uterine irritation) have been proposed as causes of luteal failure.[3] There is no doubt that vitamin A is

essential for the conversion of cholesterol to progesterone; its action can be competitively blocked by an excess of carotene. Luteolysis has been demonstrated to result from uterine irritation by a foreign object.[4] A uterine infection probably would have the same effect. (Penicillin has been found to relieve PMS, but the mechanism by which it increases progesterone and decreases estrogen and cortisone isn't clear, and probably involves endotoxin and the liver.) The IUD often causes the same kind of symptoms as the oral contraceptive pill--obesity, depression, etc., and this seems to be the result of progesterone deficiency from luteolysis. An excess of prolactin, which is now recognized as a sequel to use of the estrogen contraceptive pill (estrogen induces mitoses in the prolactin secreting pituitary cells) has been found to block progesterone synthesis. (Incidentally, Korenchevsky demonstrated 50 years ago that progesterone would cause regression of the estrogen-induced pituitary tumor.) Logically, since it isn't desirable to get pregnant during stress, the stress hormones ACTH and cortisone inhibit progesterone production. Lack of sunlight, short photoperiod, or staying indoors can probably contribute to a progesterone deficiency, since both progesterone and testosterone synthesis (the latter in men) are increased in summer.

Excessive production of estrogen can result from a large mass of adipose tissue, or from a sick liver.[5] Olfactory stimuli seem to increase estrogen production in female mice, sufficient to induce spontaneous abortion; pheromonal activation of estrogen synthesis in humans might be another possible cause of estrogen excess. [6] Stress is probably a common cause of elevated estrogen especially when it is prolonged enough to cause significant protein loss. Stress also stimulates liver estrogen synthesis.[7]

Excessive metabolism of progesterone, e.g., by its conversion to cortisol and other anti-stress hormones, can probably explain the increasingly common observations of "athlete's amenorrhea" and the development of excess facial hair in some women working under pressure (the alternate hormonal disturbance in stress appears to result in obesity).[8] Besides losing the effects of progesterone on the endometrium, pituitary gonadotrophins would be increased, and would drive various synthetic pathways at a higher rate, shifting the ratio of progesterone to other hormones, but I do not think the ovaries have been studied very much during ordinary stress. (In the stress of ionizing radiation, the ovaries produce excessive estrogen; with the stress of high levels of gonadotrophins, they tend to be cancerized.) While large doses of progesterone have been shown to have anti-stress effects without harming

the adrenals (and probably protecting them, by lowering the demand for adrenal hormones), large doses of estrogen were found to destroy certain areas of the adrenal cortex,[9] possibly in a reaction similar to luteolysis by estrogen.

4. Effects on development.

The three aspects of progesterone's biological generality discussed above disregard the time dimension, i.e., the effect of progesterone on the developing organism, which is, according to popular belief (deriving largely from its name), its only role. All of the points discussed above are relevant to the developing organism. For example, the fetus is highly dependent on glucose for growth--especially brain growth--and the oxygen supply and maternal metabolism both affect the glucose supply.

Animal studies have shown that an excess of estrogen, late in the gestation period, like oxygen deprivation and insulin-induced hypoglycemia, can cause brain damage, in the form of reduced cell number and brain weight. Stress during pregnancy can produce (apparently hormonal) defects in the offspring.[10] L. C. Strong showed transgenerational effects, apparently acting through hormone balance, in his cancer-prone (high-estrogen) mice which were treated with a liver extract (personal communication). Many older studies showed transgenerational effects which I believe can be traced to gestational hormonal modification, affecting metabolism at a variety of levels, including the liver. For example, feeding thymus to rats for several generations caused each generation to be more precocious in development. The known transgenerational influences of starvation (Zamenhoff, et al.,[11] with rats, and more recently--1978--in human studies) are similar to the first generation effects of estrogen or hypoglycemia. I suspect that these effects are part of a general system of physiologically adjusting the metabolism of offspring to the availability of nutrients.

One of the physiological effects of progesterone is its support of the thymus (opposing the effects of glucocorticoids and sex steroids). In animal experiments (dog and rat), results so far indicate that the same types of precocity are induced by progesterone in these animals as were reported for thymus feeding.[12] Dalton's (and others') studies in humans show the same generalized precocity, except that in humans the intellectual precocity is the most noticeable. Rat studies show that increased prenatal exposure to progesterone increases rats' learning ability and the thickness of their cerebral cortex, but the scientific community's

lack of interest in these studies has been great. The owner of an afghan dog which gestated with extra progesterone commented that the dog had learned to retrieve a stick by watching another dog, while "normal" afghans dislike learning anything, especially retrieving (though they have a remarkable geographic memory).

Since the brain is dependent on glucose for its growth, the ability of progesterone to promote maternal fat metabolism and to spare glucose (elevating blood glucose) for fetal use is a logical part of its role as a gestational hormone. Other pregnancy hormones, including "placental lactogen," also promote elevation of blood glucose.

I propose that there is a "developmental trajectory" (analogous to a ballistic trajectory) which is set by the availability of biological energy during gestation, and that we could, by measuring brain weight and the ratio of brain weight to body weight during gestation, predict (given stable post-natal conditions for growth) such things as the ages at puberty, full growth, and approximate lifespan. Good prenatal conditions would increase the rate of development (IQ, etc.), but would delay maturity, allowing achievement of a higher level of development by the rapid and prolonged development of higher abilities. Bright people develop faster than dull people, but bright monkeys, at first, develop even faster (see chart). Our species characteristics would include setting the angle of our developmental trajectory, but the availability of biological energy during gestation determines the rate of ascent and the "altitude" achieved, as the explosive charge determines velocity and altitude of a ballistic trajectory. The effect of nutrition on brain size is known, as are the relationships between relative brain weight and life-span[13] and between rate of sexual development and life-span (Strong, and others), so what I am suggesting is simply that the amount of energy early in life might organize in an orderly way the timing of, and quality of, development throughout the rest of one's life.

A "Medical News" item in a 1976 issue of the J.A.M.A.[14] reports a study showing that progesterone probably plays a critical role in preventing rejection of the fetus by the mother. In reviewing the scientific and medical literature, I have found no side effects attributed to natural progesterone, except for sometimes altering the menstrual rhythm temporarily. Its use before and during pregnancy is associated with a reduced incidence of birth defects. (Since all of the drugs used to treat epilepsy are known to cause birth defects, it would certainly seem reasonable to take advantage of progesterone's anti-seizure effect, especially during pregnancy. It wouldn't be hard to ascribe liability for

the prenatal injury of thousands of people, to the pharmaceutical industry and regulatory agencies, who seem to conspire to keep this information away from the medical profession.) Some publications fail to distinguish between natural progesterone and the frequently harmful synthetic progestins.

Some recent animal studies are showing that prenatal progesterone increased body size, but even more, it increased brain size, for an improved brain/body ratio. First, it was established that good prenatal nutrition produced big, healthy babies with big heads, high intelligence, and good disposition. Then, experiments with rats showed that prenatal treatment with prolactin, which stimulates progesterone synthesis in that species (but blocks it in humans) produced large brained, intelligent animals (95th percentile for brain size and intelligence). It has since been established that a large brain is associated with a long life span.

Prenatal stress produces many minor physical "stigmata," and these have been shown to be associated with hyperactivity. Excess estrogen (and other toxins, and associated deficiencies) reduces brain size and damages behavior. (In animals, the effects of prenatal stress can be passed on to the third generation.)

Progesterone opposes estrogen, and promotes prenatal nutrition. Dalton's studies of babies whose mothers received natural progesterone showed greatly improved intelligence.[15] Another researcher, deliberately attempting to improve intelligence (Dalton simply intended to treat PMS and toxemia of pregnancy) claims "his" babies have a 200 IQ. Other investigators find that progesterone babies have strong, serene, independent characters.

There is increasing recognition that prenatal conditions, whether good or bad, can be passed on to at least one subsequent generation. A reduced ability to produce progesterone is probably often a consequence of prenatal stress, which can lead to pregnancy difficulties, and another stress-injured generation. I feel that progesterone can reverse the trend toward more hyperactive and brain damaged children, and that it can make a great contribution to the mental and physical health of future generations.

5. Progesterone and magnesium.

In considering the general biological effects of progesterone, it is interesting to compare some of its functions with those of the magnesium ion, and to contrast them with the effects of calcium and estrogen.[16]

Uptake of magnesium is promoted by thyroid, and progesterone promotes thyroid function, while tending to block the stress-induced loss of magnesium. Estrogen increases the uptake of calcium.

Blood clotting (especially excessive): promoted by estrogen and calcium, restrained by magnesium and progesterone.
Blood sugar: depressed by estrogen and calcium, sustained by progesterone and magnesium.
Kidney function, diuresis: promoted by magnesium and progesterone, decreased by estrogen; excess calcium appears to damage kidneys.
Histamine release: decreased by progesterone and magnesium, increased by estrogen, and calcium probably facilitates it.
Phagocytosis and other immune functions: increased by magnesium and progesterone, decreased by estrogen; calcium is involved in triggering thymocyte death.
Glucagon: magnesium promotes, calcium inhibits.
Insulin: magnesium and progesterone restrain its secretion, calcium and estrogen promote it.
Vascular spasms: decreased by progesterone and magnesium, promoted by estrogen and calcium.
Vascular tone: stabilized by progesterone and magnesium, often decreased by estrogen, possibly acting through histamine, leading to the tendency of blood to pool in the legs. Estrogen is believed to contribute to varicose veins.
Nerve stabilization or anesthesia: magnesium and progesterone are anesthetic in very large amounts and are protective inhibitors in physiological amounts. Calcium opposes the anesthetic effect of magnesium, and is always involved in toxic or excitotoxic cell death. Estrogen even in physiological amounts is nerve-exciting, and eventually contributes to the excitotoxic death of brain cells.

Hans Selye demonstrated that calcification of various tissues (kidneys, blood vessels, and skin, for example) could be produced by interactions of stress and hormones. Selye and his associates, and F. Z. Meerson's group in Russia, have demonstrated numerous toxic interactions of iron, calcium, and unsaturated fats. Magnesium, vitamin E, thyroid, and progesterone tend to protect against those toxic effects.

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13
DOSAGE OF PROGESTERONE

Since progesterone has none of the *harmful* side effects of other hormones (except for alteration of the menstrual cycle if it is taken at the wrong time of month), the basic procedure should be to use it in sufficient quantity to make the symptoms disappear, and to time its use so that menstrual cycles are not disrupted. This normally means using it only between ovulation and menstruation unless symptoms are sufficiently serious that a missed period is not important. The basic idea of giving enough to stop the symptoms can be refined by some information on a few of the factors that condition the need for progesterone.

If a person has an enlarged thyroid gland, progesterone promotes secretion and unloading of the stored "colloid," and can bring on a temporary hyperthyroid state. This is a corrective process, and in itself isn't harmful. A thyroid supplement should be used to shrink the goiter before progesterone is given. Normal amounts of progesterone facilitate thyroid secretion, while a deficiency, with unopposed estrogen, causes the thyroid to enlarge. The production of euphoria has been mentioned as a side effect, but I think euphoria is simply an indication of a good physiological state. Very large doses that are given in vitamin E solution, allowing complete absorption, can reach the level that is sometimes achieved late in pregnancy, producing both euphoria and a degree of anesthesia. To avoid unexpected anesthesia, the correct dose should be determined by taking about 10 mg. at a time, allowing it to spread into the membranes of the mouth, and repeating the dose after 10 minutes until the symptoms are controlled.

An excessive estrogen/progesterone ratio is more generally involved in producing or aggravating symptoms than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet, other steroids, thyroid, and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia (as reported in my dissertation, University of Oregon, 1972), and this is the result of changes induced by estrogen in alveolar diffusion, peripheral vascular changes, and intracellular oxygen wastage.

Hypoxia in turn produces edema (as can be observed in the cornea when it is deprived of oxygen, as by a contact lens) and hypoglycemia (e.g., diminished ATP acts like insulin), because glycolysis must increase

greatly for even a small deficiency of oxygen. Elevated blood lactic acid is one sign of tissue hypoxia. Edema, hypoglycemia, and lactic acidemia can also be produced by other "respiratory" defects, including hypothyroidism, in which the tissue does not use enough oxygen. In hypoxia, the skin will be bluer (in thin places, such as around the eyes), than when low oxygen consumption is the main problem. Low thyroid is one cause of excess estrogen, and when high estrogen is combined with low thyroid, the skin looks relatively bloodless.

Symptoms in cycling women are most common around ovulation and in the premenstrual week, when the estrogen/progesterone ratio is normally highest. At puberty, in the early twenties and in the late thirties and menopause are the ages when the ratio is most often disturbed--and these are also the ages when thyroid disorders are commonest in women.

The individual who suffers from one aspect of the progesterone (and/or thyroid) deficiency will tend to develop other problems at different times. With cyclic depressions or migraine headaches at age 22, there will possibly be breast disease later, and often there will be problems with pregnancy. These people with a history of severe symptoms are the ones most likely to have severe problems around menopause. Prenatal exposure to poorly balanced hormones seems to predispose the child to later hormone problems.

Excess stress (which can block progesterone synthesis and elevate estrogen) may bring on symptoms in someone who never had them. Spending a summer in Alaska, with an unusually long day, may relieve the symptoms of a chronic sufferer. Dark cloudy winters in England or the Pacific Northwest are powerful stressors, and cause lower production of progesterone in women, and testosterone in men. Toxins can produce similar symptoms, as can nutritional deficiencies. A very common cause of an estrogen excess is a dietary protein deficiency--the liver simply cannot detoxify estrogen when it is under-nourished.

With a diet high in protein (e.g., 70-100 grams per day, including eggs) and vitamin A (not carotene), I have found that the dose of progesterone can be reduced each month. Using thyroid will usually reduce the amount of progesterone needed. Occasionally, a woman won't feel any effect even from 100 mg. of progesterone; I think this indicates that they need to use thyroid and diet, to normalize their estrogen, prolactin, and cortisol.

Progesterone stimulates the ovaries and adrenals to produce progesterone, and it also activates the thyroid, so one dose can sometimes have prolonged effects. It shouldn't be necessary to keep using

progesterone indefinitely, unless the ovaries have been removed. In slender post-menopausal women, 10 mg. per day is usually enough to prevent progesterone deficiency symptoms.

In a 10% solution of progesterone in vitamin E, one drop contains about three milligrams of progesterone. Normally, the body produces 10 to 20 milligrams per day. A dose of 3 or 4 drops usually brings the blood levels up to the normal range, but this dose can be repeated several times during the day if it is needed to control symptoms.

For general purposes, it is most economical and effective to take progesterone dissolved in vitamin E orally, for example taking a few drops on the lips and tongue, or rubbing it into the gums. (It is good for the general health of the gums.) These membranes are very thin, and the progesterone quickly enters the blood. When it is swallowed, the vitamin E allows it to be absorbed through the walls of the stomach and intestine, and it can be assimilated along with food, in the chylomicrons, permitting it to circulate in the blood to all of the organs before being processed by the liver. These droplets are smaller than red blood cells, and some physicians seem to forget that red blood cells pass freely through the liver.

For the topical treatment of sun damaged skin, or acne, wrinkles, etc., the oil can be applied directly to the affected area.

For topical treatment of arthritis, osteoporosis, tendinitis, bursitis, or varicose veins, to speed absorption it is best to apply a few drops of olive oil to the area, and then to rub the progesterone-vitamin E solution into and around the affected area. Some of the progesterone will be absorbed systemically, but the highest concentration is sustained in the local area, helping to correct the problem locally.

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14
AN EFFICIENT ORAL THERAPY

As early as 1912, Armour & Co. sold desiccated corpus luteum for use in cases of ovarian failure, and said that it prevented "nervous symptoms accompanying" menstrual abnormalities.[1] It was also used to treat obesity and other physical conditions sometimes associated with "ovarian deficiency."

In early reports on the use of synthetic progestins, they were praised as being active when taken orally, unlike natural progesterone, which was said to be "destroyed in the stomach." Although I have looked carefully, I have never found the study which demonstrated that progesterone was inactive when taken orally. No source was cited for the claim. I am convinced that the idea was invented by the promoters of the patented new compounds. The most "popular" (i.e., profitable) of the synthetic "progestins," medroxyprogesterone acetate, is not a progestagen, causes cancer, impairs circulation to the heart, causes birth defects, and suppresses the production of progesterone. I feel that the involvement of the various government agencies in the promotion of this poison, and the suppression of information about natural progesterone, has been conspiratorial and deliberately criminal, and those involved should be identified as criminals.

When fats are eaten, they are almost 100% absorbed by the small intestine. They break up in the intestine into microscopic droplets, called chylomicrons, and reach the general circulation in that form. If progesterone is perfectly dissolved in oil, it is absorbed in that way, and is not immediately exposed to enzymes in the wall of the intestine or in the liver. People often speak of "avoiding the liver on the first pass," but in fact chylomicrons pass through the liver many times before they are destroyed; after an hour, at least 10% of the chylomicrons are still circulating.

While dissolved progesterone circulates in the chylomicrons, it will be distributed to the various tissues. Unlike other steroid hormones, progesterone tends to become concentrated inside cells. Its concentration in red blood cells is twice as high as its concentration in serum,[2] and the brain contains a still higher concentration. These intracellular reservoirs of progesterone prolong the elevated blood levels, so that the observed hormone level after a single oral dose is much more stable than are the triglyceride levels after a fatty meal. The perfect absorption, and the

prolonged action make the oil-dissolved oral progesterone much more efficient and economical than injected or suppository forms.

Since progesterone tends to promote its own synthesis, it shouldn't be necessary to keep using it, unless the ovaries have been removed, or the thyroid or cholesterol level is very low, or aging has damaged their ability to convert cholesterol to progesterone. While an excess of carotene can inhibit progesterone synthesis, a carrot salad (grated carrots, vinegar, coconut oil, and salt) can often help to normalize progesterone, apparently by protecting against intestinal absorption of bacterial endotoxin, and by helping to reduce the reabsorption of estrogen which has been excreted in the bile.

The beneficial hormonal effects that have been seen during antibiotic therapy (raising progesterone while lowering cortisol and estrogen) can be achieved safely with the carrot salad in most cases, without the possible toxic effects of the antibiotics.

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15
TRANSDERMAL PROGESTERONE FOR PREMENSTRUAL SYNDROME

For many years, Katharina Dalton studied the use of injected progesterone as therapy for the premenstrual syndrome. A typical patient required several progesterone injections per month, more or less permanently. While this was feasible in her practice in London, it is not comfortable or convenient, in some cases leads to serious reactions at the injection sites, and in the United States would be too expensive for general use. When the syndrome is disabling, even the burden of frequent and expensive injections was usually seen as a welcome alternative. However, a less expensive and more pleasant form of administration could make the therapy available to millions of women who are now disabled for one or more days each month. A satisfactory alternative to injections for many women is to use a dissolved form of progesterone in a vitamin E base for transdermal use. (This form is especially suitable for treating localized problems, including arthritis, varicose veins, and facial or body hair that has developed from excess androgens.)

After animal experiments revealed that progesterone in vegetable oil was absorbed effectively through the skin, in 1977 I began experiments with women who suffered with the premenstrual syndrome. The first three were completely disabled by epilepsy, suicidal depression, and optical neuritis, and they all had dramatic, immediate recoveries.

The effectiveness of the transdermal absorption route of administration varies with the individual, but compares favorably with injections in the amount assimilated. (Neither method is as economical as oral use.) Thickness of skin or degree of circulation in the skin (these can be very abnormal in hypothyroidism, for example) and the amount of adipose tissue apparently make some difference in the rate of absorption and response. When a small daily dose (e.g., 5 or 10 mg.) is sufficient, this can be taken as about 1/8 teaspoonful of a 10 percent solution rubbed into the skin, for example on the front of the neck, or the inside of the arms, where the skin is thin, after having spread a few drops of olive oil or coconut oil over the skin to make the viscous solution spread more easily. For large doses, the appropriate amount can be applied to a larger area of skin after a hot bath, once or twice a day if necessary.

Although progesterone will dissolve in warm vegetable oil, when the oil cools nearly all of the progesterone crystallizes out of solution. This is why vitamin E is necessary as the solvent, for transdermal use as well as oral use.

Over the years I have seen transdermal progesterone used in hundreds of women suffering from the full range of perimenstrual symptoms, including migraine, acne, depression, mastalgia, edema, and lethargy. Nearly all the women, applying the lotion themselves, are able to find the appropriate dosage for controlling their symptoms.

Often thyroid therapy or a change in diet or light-exposure or amount of activity is necessary for complete relief from symptoms. Progesterone therapy can offer quick relief to many people whose real problem is diet-induced hypothyroidism, but it shouldn't be considered as a substitute for the correct diet, or for thyroid supplementation when that is needed.

It is necessary to be clear in describing the amounts that can be used, while leaving it up to the patient to find the dose which controls her symptoms, because some women have an exaggerated idea of the power of a "hormone." The behind-the-ear scopolamine patch has had its influence on the idea of transdermal therapy, and many women have tried just touching the oil to their wrists.

It is sometimes helpful for the physician to administer one dose (sometimes using a twenty percent solution) in the office, and to wait 30 or 40 minutes to make sure that it was large enough to take effect. Once having felt sudden relief from the correct dose, it is easier for the patient to understand how it should be used. (This trial dose in the office is a good idea when using oral doses, too, but for an additional reason, namely, to watch for signs of an overdose. It is probably impossible to overdose using the transdermal method.)

Many of the solvents which hold progesterone stably in a concentrated solution are highly allergenic. Injectable progesterone in oil could be used transdermally except for this problem. If necessary, micropulverized progesterone can be dissolved in warm olive oil for patients who react to other materials, or who have a history of skin allergies. Progesterone usually corrects such allergies, but some women have found that taking it orally in oil was preferable.

The French have two standard topical progesterone preparations that have been used for many years for breast pain and facial hair.

Besides the slow and steady absorption permitted by the transdermal method, and the fact that many women with PMS are

exaggeratedly sensitive to ingesting anything that tastes odd, there is a special set of problems that make the topical use of progesterone very valuable. As I mentioned above, the French advocate topical progesterone for mastalgia, but I think thyroid supplementation is the more general solution to that problem. But in the case of bursitis, arthritis, tendonitis, "fibrositis," and varicose veins, it is possible to achieve a higher local concentration with transdermal use, than can conveniently be achieved by oral administration. (Though the two can be combined usefully.)

As with oral progesterone, it is important to correct a goiter before using transdermal progesterone, because progesterone acts directly on the thyroid gland to facilite its secretion, and the sudden correction of thyroid function can lead to a hyperthyroid state, as the goiter unloads the stored hormone.

Progesterone is so insoluble in water that it can penetrate tissue to a remarkable depth, before a significant amount of it is carried away in the body fluids. Tissue proteins have a great affinity for oils. Failure to consider these points has made many people doubt that topical treatment could affect the underlying tissues.

16
THE PROGESTERONE DECEPTIONS

In the 1930s, it was demonstrated that estrogen, even in small doses, produced abortions, and that when it is given early enough, even a very small dose will prevent implantation of the fertilized embryo. Progesterone was known, by the early 1940s, to protect against the many toxic effects of estrogen, including abortion, but it was also known as nature's contraceptive, since it prevents pregnancy without harmful side-effects, by different mechanisms, including prevention of sperm entry into the uterus. That is, progesterone prevents the miscarriages which result from excess estrogen,(1,2) but if used before intercourse, it prevents conception, and thus is a true contraceptive, while estrogen is an abortifacient, not a contraceptive.

In the 1950s, there was a search for chemicals which would prevent ovulation. According to Carl Djerassi,(3) drug companies were extremely reluctant to risk a religious backlash against their other products, and so hesitated to market contraceptives. Obviously, the induction of monthly abortions would have been even harder to sell.

According to Djerassi,(3) "Until the middle 1940s it was assumed that progesterone's biological activity was extremely specific and that almost any alteration of the molecule would diminish or abolish its activity." This would obviously discourage interest from the drug companies, who could patent a substance which they had chemically modified, but could not patent a simple natural substance. However, many substances--even non-steroidal chemicals--turned out to have estrogenic action.(4)

By 1942, Hans Selye had demonstrated that natural steroids retain their activity when administered orally. But every drug company with a steroid patent had an obvious interest in having the public believe that there is a reason that the natural steroids cannot be conveniently used. The doctrine that natural steroids are destroyed by stomach acid appeared, was promoted, and was accepted. In the manufacture of progesterone, the precursor steroid is boiled in hydrochloric acid to free it from its glucose residue; no one seriously believed that stomach acid hurts progesterone, except the public.

The real issue is solubility. Hydrocortisone is reasonably soluble in water, but progesterone is extremely insoluble in water, and, though it is

vastly more soluble in vegetable oil than in water, it does not stay in solution at room temperature even at the low concentration of 1 part in 1000 parts of vegetable oil.

When people speak of an allergy to progesterone (or even to penicillin) they generally are not aware of the presence of a very toxic solvent.(5) A few years ago, progesterone was often sold dissolved in benzyl benzoate; the Physician's Desk Reference warned of possible allergic reaction to progesterone. Now, it is supposedly sold dissolved in vegetable oil, with about 10% benzyl alcohol as a bacteriostatic agent. Bacteriostatic water contains 0.9% to 1.9% benzyl alcohol, and can irreversibly harm nerves.(6,7) Awareness of benzyl alcohol's toxicity goes back to 1918 at least; it was proposed as an effective insecticide, and was found to be toxic to many animal systems. The safe systemic dose(7) is exceeded with an injection of 150 mg. of progesterone, yet the local concentration is far higher. It can cause a severe reaction even when used at a lower concentration, in bacteriostatic water.(5)

Other alcohols, including ethanol, have been used as solvents, but since they (ethanol even more than benzyl alcohol) have an affinity for water, the solution decomposes in contact with tissue water.

In spite of the toxicity of the vehicle, several beneficial effects can be obtained with injected progesterone, in serious conditions such as epilepsy or cancer of the breast or uterus. Many researchers have commented on the very obvious difficulty of giving very large amounts of progesterone.(8) My comparisons of oral progesterone in tocopherol with other forms and methods of administration show a roughly similar efficiency for oral and injected progesterone, and about 1/20 the effect for suppositories. Crystals of progesterone are visible in the suppositories I have examined, and this material is obviously wasted.

An old theory of vitamin E's mechanism of action in improving fertility was that it spares progesterone.(9) It is established that some of the effects of vitamin E and progesterone are similar; for example, both prevent oxygen waste and appear to improve mitochondrial coupling of phosphorylation with respiration. I suspected that if they actually both work at the same mitochondrial site, then they must have a high mutual solubility. Knowing the long-standing problem of administering large doses of progesterone without a toxic solvent, I applied for and was granted a patent for the composition of progesterone in tocopherol. One of my reasons for publishing in the form of patents is that I have had many years of experience in having my discoveries taken up by others without acknowledgment. My dissertation research, which established

that an estrogen excess kills the embryo by suffocation, and that progesterone protects the embryo by promoting the delivery of both oxygen and glucose, didn't strike a responsive chord in the journals which are heavily influenced by funds from the drug industry.

According to a consultant for a major medical journal, the idea "...of dissolving progesterone, a fat soluble steroid hormone, in vitamin E which is then incorporated into chylomicrons absorbed via the lymphatics, and thus avoids the liver on the so called first pass... ...is so simple it is amazing that the pharmaceutical companies have not jumped on it."

In the powder form, direct and intimate contact with a mucous membrane allows lipid phase to lipid phase transfer of progesterone molecules. Instead of by-passing the liver, much of the progesterone is picked up in the portal circulation, where a major part of it is glucuronidated, and made water soluble for prompt excretion. Since this glucuronide form cross-reacts to some extent with ordinary progesterone in the assay process, and since 50% of the ordinary free progesterone is carried inside the red blood cells,(10, 11) and 50% is associated with proteins in the plasma, while the glucuronide hardly enters the red blood cells at all, it is better to judge by clinical efficacy when comparing different oral forms. My comparisons show several times higher potency in the tocopherol composition than in powder form.

Since progesterone's use as a drug antedates the 1938 law requiring special federal approval, its legal status is similar to that of thyroid hormone. Unfortunately, for both thyroid and progesterone, there is a tendency to cut corners for the sake of a bigger profit margin.

For example, steroid acetates are generally a little cheaper than the simple natural steroid. Some people assume that an acetate or butyrate can be substituted for the steroid itself. This can cause dangerous reactions.

Medroxyprogesterone acetate is considered a progestin (though it is not supportive of gestation), because it modifies the uterus in approximately the way progesterone does, but it is luteolytic, and lowers the ovaries' production of progesterone while progesterone itself has a positive effect on the corpus luteum, stimulating progesterone synthesis. Defining "progestin" in a narrow way allows many synthetics to be sold as progestagens, though some of them are strongly estrogenic, allowing them to function as contraceptives--it is odd that contraceptives and agents which suppress progesterone synthesis should be officially called "supporters of pregnancy." It is probably partly the acetate group in the medroxyprogesterone acetate molecule which makes it bind firmly to

receptors, yet causes it to block the enzymes which would normally be involved in progesterone metabolism. (I think testosterone, even, might be a safer progestin than medroxyprogesterone acetate.) Pregnenolone acetate similarly blocks the enzymes which normally metabolize pregnenolone.(12) In aspirin, it has been found that it is the acetyl group which (by a free radical action) blocks an enzyme involved in prostaglandin synthesis.

If the category called "progestogens" or "progestins" is to be defined on the basis of a single tissue reaction, then it is possible to classify progesterone with the toxic synthetic substances, but then it becomes highly deceptive to imply that progesterone is *just* a progestin, or that it has any of the *other properties* of the toxic synthetics, but this continues to be done. The warnings about "progestins causing birth defects," for example, cause epileptic women to use conventional anti-seizure drugs (all of which cause birth defects) during pregnancy, and to avoid natural progesterone, which generally could control their seizures. Thus, a false message attached to progesterone creates precisely the harm it claims to want to prevent. In my communications with the regulatory agencies, I have concluded that their attempts to deceive are too blatant to ascribe to incompetency. Whether it's the Forest Service or the FDA, the principle is the same: the regulatory agencies have been captured by the regulated industries.

Another place to cut costs is in the tocopherol. Tocopherol acetate does have vitamin E activity, but since it is only about half as efficiently absorbed as the simple tocopherol,(13) it is a mistake to save a few dollars an ounce, at the expense of losing half of the therapeutic effect. People who have compared natural progesterone in natural tocopherols with other compositions have insisted that the other compositions must not contain progesterone.

The taste of natural vitamin E is stronger than that of the synthetic forms, but since the mixture is absorbed by any tissue it contacts, including various parts of the bowel, it can be taken in a capsule. If a small amount of olive oil is used with it, absorption through the skin is very rapid. Many women use it vaginally, spread onto a diaphragm, to hold it in contact with the membranes. The efficiency of absorption by all routes is so high that patients should be warned against its anesthetic effect, until their dosage requirement is known approximately. Some physicians prefer concentrations higher than 10%, but the risk of accidental drunkenness or anesthesia is higher with the stronger solutions.

It is an indication of the tocopherol solution's high availability that medical researchers such as Roy Hertz,(8) who thought they were administering maximal doses by combining injections with suppositories, never mentioned the problem of an anesthetic effect from an overdose. Similarly, it is evidence of the extremely poor availability of the micropulverized progesterone that the researchers have administered hundreds of milligrams per day, without mentioning the symptoms of an overdose. Because of the difficulties involved in scientifically studying the clinical effectiveness of various formulations, I think the most practical way of evaluating the effectiveness of different progesterone formulations is to measure the amount extractable from the red blood cells, a few hours after the peak serum level has been reached. This will reasonably reflect the amounts reaching brain cells, adrenal glands, and the various other cells on which progesterone has its therapeutic action.

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17
PRESERVING THE TISSUES: Osteoporosis and the Skin

While I was working on my dissertation, around 1970, the opposition between stress-injury and energetic resistance became increasingly apparent to me. Estrogen (like X-irradiation, aging, or trauma) called up the cortisone response, and other factors, especially progesterone and thyroid, allowed the organism to restore itself in ways that neutralized the cortisone response. Therefore, when I saw that the estrogen-like processes became more and more dominant after middle-age, it was natural to think of progesterone and thyroid as the main factors that should be replaced. This is why in 1975 I described menopause as resembling Cushing's syndrome, which is caused by a toxic excess of cortisol. Osteoporosis, hot flashes, insomnia, and mood disorders are caused by cortisol, and so I tried using progesterone and thyroid--the anticortisol factors--for those conditions. The results were so profound that I began to study the general implications for health, and to try to understand the mechanisms so that prevention might replace treatment.

Several people who had been abandoned as hopeless terminal cases--with "epileptic brain damage," inflammatory degeneration of hip and thigh bones, diabetic gangrene, senility--recovered their health within a few days, and went on with their lives in productive and pleasant ways.

I knew that intense and frequent epileptic seizures cause the exhaustion and death of brain cells. A 52 year old woman had been having seizures for over 15 years. Her neurologist gave her a mental exam every year, and considered her to be hopelessly demented. After using progesterone for a few days, she functioned normally. After about a year, she returned to graduate school at the University of Oregon, and got a master's degree with straight As.

A 79 year old woman had had artificial hip joints implanted when she was in her fifties, but her bones had weakened to the point that no further surgical repair was possible. She settled her affairs, and didn't expect to get out of bed again. After using progesterone topically and orally, after two weeks she was able to get out of bed and return to her

normal activities. At the age of 85, she went camping on the beach in Mexico, and travelled to Scotland.

An 82 year old man was agitated and confused, and was apparently suffering from senile dementia. After being given progesterone and pregnenolone for a few days, his mind became clear, and he returned to work on scientific projects he had begun decades earlier. A squamous cell cancer on his lip regressed, and never bothered him again.

A 60 year old woman had "osteoporosis" (shrinking) of the jaw bone that was causing her teeth to loosen. After applying progesterone solution to her gums daily for a few months, her teeth became firm.

When bones had almost disappeared from X-rays, yet became firm and functional within a few weeks, it was obvious that regeneration had taken place. But when brains went in a very short time from imbecility or idiocy to intellectual productivity, I could only guess what might be happening to the cells. But I got a useful perspective on the mechanism of progesterone's action by seeing some recoveries that were even faster than those I have mentioned.

In animal experiments, I knew that estrogen causes cells to take up water within a few minutes after it reaches the tissue, and that this is at least partly the result of its interfering with the availability of oxygen. Within 40 minutes of administering a large dose of estrogen, the lungs become extremely inefficient at oxygenating the blood. This involves a sudden thickening of the alveolar membranes and the walls of capillaries, simply by taking up water. So, when I saw bulging veins disappear a few minutes after women took progesterone, along with a sudden lifting of extreme depression, I guessed that their circulation had become more efficient, and that better oxygenation had changed their mood.

Then, I repeatedly saw physical changes in other people that were visible within an hour, and that involved a sudden movement of water out of edematous tissues. In many people with damaged joint cartilage (confirmed by various types of examination, including arthroscopy), the joints became mobile in an hour, and by the next day, the defect no longer existed. A man who was purple from emphysema changed color within a few hours, and within a few days was going to work. The bulging eyes of exophthalmic Graves' disease receded into their sockets noticeably within an hour, and were normal the next day. Simply improving the circulation couldn't have done those things. Opposing estrogen's edema-promoting action was involved, but I couldn't imagine any mechanism that could

explain such rapid movement of water from the swollen tissue into the blood stream.

One of estrogen's effects is to lower the amount of albumin in the blood. Estrogen causes the liver to synthesize less albumin, partly by causing the messenger RNA to be destabilized and degraded. (Iron can have some similar effects on liver RNA.) When there isn't enough albumin in the blood, water moves from the blood into the tissues. Albumin binds oily substances, and its conformation seems to be opened when it binds them. Progesterone is known to adsorb strongly to proteins--it has been called a "cardinal adsorbant," meaning that it can bind in ways that cause the protein's adsorptive capacity to change. I believe that progesterone and pregnenolone oppose estrogen in many ways, but the amazing speed with which they can cause major structural changes in the soft tissues convinces me that one of their first sites of action is the albumin molecule, causing its conformation to open in such a way that it is able to more strongly bind water molecules. This physical change in albumin would change the blood's osmotic/oncotic pressure, causing water to flow into capillaries. As the edema is reduced, oxygenation is more efficient, because the pathway for oxygen diffusion becomes shorter.

Albumin has been described as a first line of defense against toxins, since it binds them until the liver is able to degrade them chemically. Progesterone, pregnenolone, and cholesterol are known to increase the organism's resistance to a great variety of toxins. (Selye coined the name "catatoxic steroids" to describe steroids of this type.) If these steroids bind to albumin in a way that opens the protein to increase its binding capacity, that single process could explain the "catatoxic" effect, as well as the anti-edema effect.

When the blood is unable to retain its normal amount of water because of insufficient albumin/sodium, the blood volume is reduced as the tissues become water-logged. This causes the hematocrit (the proportion of cells in a volume of blood) to rise, and this increased packing of red blood cells causes the blood to become more viscous. (Knisely studied this phenomenon in a great variety of sickness.) Increased viscosity and slower flow decreases the bloods ability to deliver oxygen and nutrients to the tissues, including the blood vessel walls, modifying their tone. Slower flow, even without any changes in the fibrin-fibrinogen system itself, increases the formation of clots.

This description of progesterone's immediate action is intended to take some of the mystery out of its dramatic effects, but it isn't intended

to argue against any of its actions within cells. It serves to give a general picture of how progesterone can systematically reduce stress and its harmful consequences, just by making blood circulation more efficient.

At first I most often used progesterone dissolved in olive oil to stop the stress-induced processes of deterioration, with a high protein diet to support the processes of repair. Now, I have added a variety of other techniques, including the use of progesterone in vitamin E.

There always seems to be a rough balance between tissue regeneration and tissue degeneration, with growth and repair occurring when the equilibrium shifts in one direction, and with atrophy or degeneration occurring when the balance shifts in the other direction. If we can understand the mechanisms of atrophy, and how to retard or to block tissue destruction, then we can restore the balance to a degree which might allow regeneration to occur, even if we don't clearly understand the mechanisms of growth.

Skin and bones are such different types of tissue that it will be useful to start with them, because if we can see similar processes of degeneration or regeneration in them, then the chances are good that the same processes will occur in other tissues too. Bone is a relatively stable tissue, while skin is a tissue whose cells divide rapidly.

It is common medical knowledge that cortisone and related glucocorticoid-type hormones cause skin to atrophy, becoming thinner. Using topical applications of a synthetic derivative of cortisone, C. M. Papa and A M. Kligman showed that the atrophy extended to the pigment cells, reducing their size and eliminating most of their dendritic branches. They also found that estrogen suppressed sweating and hair growth. The other steroids they tested, progesterone, testosterone, and pregnenolone, acted in the opposite direction, making aged and atrophied skin thicker and more regular. They also made the pigment cells larger, and increased their branching.[1]

Since these hormones were already known to have protective actions against cortisone and estrogen, these results were not too surprising, though they did directly contradict the claims of people who made estrogen-containing cosmetics.

Since progesterone and pregnenolone do not cause healthy, young skin to thicken, their effect in damaged skin is probably partly to replace the deficiency of that type of steroid which occurs with aging, and to offset the damaging effects of the catabolic hormones, whose influence does not decrease with age.[2]

Many years ago it was found that in old age a woman's estrogens were increased relative to the 17-keto steroids adrenal androgens. Later, it was found that the conversion of androgen to estrogen increases with age in both men and women, and that this occurs largely in fat cells. Several years ago, P. K. Siiteri found that low thyroid modified the enzymes of fat cells in a way that would tend to increase the conversion of androgen to estrogen. More recently, it was found that adding progesterone to the enzymes had the opposite effect of aging and hypothyroidism, protecting the androgen from conversion to estrogen. These researchers (C. J. Newton and colleagues, of London) concluded that the decreased output of progesterone after the menopause might account for the increased production of estrogen.[3] Since progesterone declines in aging men, too, this could account for the same process in men.[2]

Vitamin A's effect on the skin opposes that of estrogen.[4] There are several mechanisms that could account for this. Vitamin A is used in the formation of steroids, and since the skin is a major site of steroid metabolism, vitamin A might help to maintain the level of the anti-catabolic steroids. A deficiency of vitamin A causes excessive release of the lysosomal enzymes, acid hydrolases, resulting in tissue catabolism.[5] Also, vitamin A is necessary for the proper differentiation of cells in skin and other membranes. A deficiency tends to cause an increased rate of cell division, with the production of abnormal cells, and a substitution of keratinized cells for other types. Estrogen also promotes keratinization and speeds cell division. A deficiency of vitamin A can cause leukoplakia in the mouth and on the cervix of the uterus; although this is considered "pre-cancerous," I have found it to be very easily reversible, as I have discussed elsewhere.[6] I suspect that the intracellular fiber, keratin, is produced when a cell can't afford to do anything more complex. Adequate vitamin A speeds protein synthesis,[7] and allows it to be used more efficiently.

Prolactin (which is promoted by estrogen, and inhibited by progesterone) increases with stress and with age. It probably affects every tissue, but it seems to have its greatest efects on the secretory membranes. It is known to have strong effects on the kidney, gut and skin (sweat and oil glands, hair follicles, and feathers inbirds), and on the gills of fish. Its involvement with milk production suggests that it might mobilize calcium from bones, and inf fact it does contribute to osteoporosis. This was foreseen by G. Bourne, in his book on the

metabolism of hard tissues, when he suggested that estrogen, acting through the pituitary, might be expected to promote osteoporosis.

Since reading Bourne's book, I have doubted that it was rational to use estrogen to prevent osteoporosis, especially when it is known to be carcinogenic and when the ratio of estrogen to and androgens and progesterone increases after menopause. Now that several publications have appeared clearly showing that estrogen increases prolactin, that prolactin increases with aging, and that prolactin contributes to osteoporosis, the postmenopausal use of estrogen is worse than dubious. But this was exactly when the pharmaceutical companies needed help in continuing to sell their profitable estrogens, and this was exactly the time when the FDA came out with its official approval of estrogen for preventing osteoporosis.[8]

Some doctors combine estrogen with testosterone, and this is much safer and more likely to keep the bones healthy. But since testosterone, like estrogen and cortisone, causes the thymus gland to atrophy, it is not a very good idea for chronic use, even if it doesn't cause masculinization. The other anti-estrogens, which are present at high levels in young women, include progesterone and DHEA. I have seen several publications which I think would justify the use of physiological amounts of DHEA to prevent or to treat osteoporosis,[9] and a few which support the use of progesterone.[10] My own observations on their use in osteoporosis have been presented many times at alternative medical conferences since the 1970s, but the main-line medical journals and conferences have declined to accept my reports, even when they advertise that all papers submitted will be presented in some form; many physicians believe that they are being presented with a fair sampling of the work being done in endocrinology, when in fact they are being given intensive advertising sessions.

Since it is known that cortisol causes bone loss, and it is widely accepted that progesterone has an "antiglucocorticoid" action, it is reasonable to think that progesterone should protect against bone loss, and that it is a progesterone deficiency after menopause which is a major factor in the ddevelopment of osteoporosis. In the first edition of *Nutrition for Women* (1975) I pointed this out, in comparing menopause to Cushing's disease. Nencioni and Polvani have more recently made observations which support this mechanism, in which progesterone "exerts a protective effect," by blocking the corticosteroid receptors. They observed "that the process of rapid bone resorption starts before the

onset of amenorrhea and the abrupt fall in the estrogen levels and coincides with decline in progesterone secretion."

By improving circulation of the blood and oxygenation of the tissues, progesterone and pregnenolone will decrease the need for the body to produce cortisol. Pregnenolone acts in the brain to lower the basal secretion of ACTH. This protective effect is more basic than that achieved by blocking the cortisol receptors.

The early tests of the toxicity of vitamin A used cartilage in tissue culture. The same enzymes which are released by a deficiency of vitamin A are released by a large excess, causing dissolution of the cartilage. Other studies showed that a vitamin A deificiency caused similar changes in both bone and cartilage. Although much vitamin A is consumed in the production of progesterone, these studies show a direct effect of the vitamin on tissue stability. Although I believe that a vitamin A supplement will offer considerable protection against osteoporosis (and also against aging of the skin), it is important to remember that excessive vitamin A inhibits the thyroid, and that there is less risk of toxicity when vitamin E is supplemented too. I think many of the headaches currently associated with vitamin A use are the result of a preservative in the capsules (probably a sulfite), since people who reast to the vitamin in capsule form don't react when they use a specially ordered bulk form prepared without preservatives.

Things which damage skin and bones also damage other tissues, and things which protect them also protect other tissues. The protective factors include hormones (thyroid, DHEA, progesterone, and pregnenolone), vitamins A and E, and minerals--including magnesium, calcium, and sodium. Sodium spares magnesium, and helps to make albumin function in regulating blood and tissue water content. Under some conditions, sodium can act as an antioxidant. Since the unsaturated oils (and their prostaglandin derivatives) decrease respiration, cause stress to be more harmful, and have some specific effects that promote aging of skin, bones, and other tissues, the use of coconut oil is especially important. I think its use is one of the factors that prevents osteoporosis in tropical countries.

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18
ARTHRITIS AND NATURAL HORMONES

A very healthy 71 year-old man was under his house repairing the foundation, when a support slipped and let the house fall far enough to break some facial bones. During his recovery, he developed arthritis in his hands. It is fairly common for arthritis to appear shortly after an accident, a shock, or surgery, and Han Selye's famous work with rats shows that when stress exhausts the adrenal glands (so they are unable to produce normal amounts of cortisone and related steroid hormones), arthritis and other "degenerative" diseases are likely to develop.

But when this man went to his doctor to "get something for his arthritis," he was annoyed that the doctor insisted on giving him a complete physical exam, and wouldn't give him a shot of cortisone. The examination showed low thyroid function, and the doctor prescribed a supplement of thyroid extract, explaining that arthritis is one of the many symptoms of hypothyroidism. The patient agreed to take the thyroid, but for several days he grumbled about the doctor 'fixing something that wasn't wrong' with him, and ignoring his arthritis. But in less than two weeks, the arthritis had entirely disappeared. He lived to be 89, without a recurrence of arthritis. (He died iatrogenically, while in good health.)

Selye's work with the diseases of stress, and the anti-stress hormones of the adrenal cortex, helped many scientists to think more clearly about the interaction of the organism with its environment, but it has led others to focus too narrowly on hormones of the adrenal cortex (such as cortisol and cortisone), and to forget the older knowledge about natural resistance. There are probably only a few physicians now practicing who would remember to check for hypothyroidism in an arthritis patient, or in other stress-related conditions. Hypothyroidism is a common cause of adrenal insufficiency, but it also has some direct effects on joint tissues. In chronic hypothyroidism (myxedema and cretinism), knees and elbows are often bent abnormally.

By the 1930's, it was well established that the resistance of the organism depended on the energy produced by respiration under the influence of the thyroid gland, as well as on the adrenal hormones, and that the hormones of pregnancy (especially progesterone) could substitute for the adrenal hormones. In a sense, the thyroid hormone is the basic anti-stress hormone, since it is required for the production of the adrenal and pregnancy hormones.

A contemporary researcher, F. Z. Meerson, is putting together a picture of the biological processes involved in adapting to stress, including energy production, nutrition, hormones, and changes in cell structure.

While one of Selye's earliest observations related gastrointestinal bleeding to stress, Meerson's work has revealed in a detailed way how the usually beneficial hormone of adaptation, cortisone, can cause so many other harmful effects when its action is too prolonged or too intense.

Some of the harmful effects of the cortisone class of drugs (other than gastro-intestinal bleeding) are: Hypertension, osteoporosis, delayed healing, atrophy of the skin, convulsions, cataracts, glaucoma, protruding eyes, psychic derangements, menstrual irregularities, and loss of immunity allowing infections (or cancer) to spread.

While normal thyroid function is required for the secretion of the adrenal hormones, the basic signal which causes cortisone to be formed is a drop in the blood glucose level. The increased energy requirement of any stress tends to cause the blood sugar to fall slightly, but hypothyroidism itself tends to depress blood sugar.

The person with low thyroid function is more likely than a normal person to require cortisone to cope with a certain amount of stress. However, if large amounts of cortisone are produced for a long time, the toxic effects of the hormone begin to appear. According to Meerson, heart attacks are provoked and aggravated by the cortisone produced during stress. (Meerson and his colleagues have demonstrated that the progress of a heart attack can be halted by a treatment including natural substances such as vitamin E and magnesium.)

While hypothyroidism makes the body require more cortisone to sustain blood sugar and energy production, it also limits the ability to produce cortisone, so in some cases stress produces symptoms resulting from a deficiency of cortisone, including various forms of arthritis and more generalized types of chronic inflammation.

Often, a small physiological dose of natural hydrocortisone can help the patient meet the stress, without causing harmful side-effects. While treating the symptoms with cortisone for a short time, it is important to try to learn the basic cause of the problem, by checking for hypothyroidism, vitamin A deficiency, protein deficiency, a lack of sunlight, etc. (I suspect that light on the skin directly increases the skin's production of steroids, without depending on other organs. Different steroids probably involve different frequencies of light, but orange and red light seem to be important frequencies.) Using cortisone in this way,

physiologically rather than pharmacologically, it is not likely to cause the serious problems mentioned above.

Stress-induced cortisone deficiency is thought to be a factor in a great variety of unpleasant conditions, from allergies to ulcerative colitis, and in many forms of arthritis. The stress which can cause a cortisone deficiency is even more likely to disturb formation of progesterone and thyroid hormone, so the fact that cortisone can relieve symptoms does not mean that it has corrected the problem.

According to the Physicians' Desk Referenc, hormones similar to cortisone are useful for treating rheumatoid arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, acute gouty arthritis, acute nonspecific tenosynovitis, psoriatic arthritis, ankylosing spondylitis, acute and subacute bursitis, and epicondylitis.

Although cortisone supplementation can help in a great variety of stress-related diseases, no curewill take place unless the basic cause is discovered. Besides the thyroid, the other class of adaptive hormones which are often out of balance in the diseases of stress, is the group of hormones produced mainly by the gonads: the "reproductive hormones." During pregnancy these hormones serve to protect the developing baby from the stresses suffered by the mother, but the same hormones function as part to the protective anti-stress system in the non-pregnant individual, though at a lower level.

Some forms of arthritis are known to improve or even to disappear during pregnancy. As mentioned above, the hormones of pregnancy can make up for a lack of adrenal cortex hormones. During a healthy pregnancy, many hormones are present in increased amounts, including the thyroid hormones. Progesterone, which is the most abundant hormone of pregnancy, has both anti-inflammatory and anesthetic actions, which would be of obvious benefit in arthritis.

There are other naturally anesthetic hormones which are increased during pregnancy, including DHEA, which is being studied for its anti-aging, anti-cancer, and anti-obesity effects. (One of the reasons that is frequently given for the fact that this hormone hasn't been studied more widely is that, as a natural substance, it has not been monopolized by a drug patent, and so no drug company has been willing to invest money in studying its medical uses.) These hormones also have the ability to control cell division, which would be important in forms of arthritis that involve invasive tissue growth.

While these substances, so abundant in pregnancy, have the ability to substitute for cortisone, they can also be used by the adrenal glands to

produce cortisol and related hormones. But probably the most surprising property of these natural steroids is that they protect against the toxic side-effects of excessive adrenal hormones. And they seem to have no side-effects of their own; after about fifty years of medical use, no toxic side effects have been found for progesterone or pregnenolone.

Pregnenolone is the material the body uses to form either progesterone or DHEA. Others, including DHEA, haven't been studied for so long, but the high levels which are normally present in healthy people would suggest that replacement doses, to restore those normal levels, would not be likely to produce toxic side effects. And, considering the terrible side effects of the drugs that are now widely used, these drugs would be justifiable simply to prevent some
of the toxic effects of conventional treatment.

It takes a new way of thinking to understand that these protective substances protect against an excess of the adrenal steroids, as well as making up for a deficiency. Several of these natural hormones also have a protective action against various poisons; Selye called this their "catatoxic" effect.

Besides many people whose arthritis improved with only thyroid supplementation, I have seen 30 people use one or more of these other natural hormones for various types of arthritis, usually with a topical application. Often the pain is relieved within a few minutes. I know of several other people who used progesterone topically for inflamed tendons, damaged cartilage, or other inflammations. Only one of these, a woman with rheumatoid arthritis in many joints, had no significant improvement. Though she used only a small amount, an hour after she had applied it to her hands and feet, she enthusiastically reported that her ankle had stopped hurting, but after this she said she had no noticeable improvement.

We often hear that "there is no cure for arthritis, because the causes are not known." If the cause is an imbalance in the normal hormones of adaptation and resistance, then eliminating the cause by restoring balance will produce a true cure. But if it is more profitable to sell powerful drugs than to sell the nutrients needed to form natural hormones (or to supplement those natural hormones) we can't expect the drug companies to spend any money investigating that sort of cure. And at present the arthritis market amounts to billions of dollars in drug sales each year.

Fasting has been found to relieve rheumatoid arthritis, and there is good evidence that a variety of bowel bacteria are involved in arthritis

and other "autoimmune diseases." Bacterial toxins and antigens interact with hormones and the immune systems, and intestinal health should be considered as an integral part of hormone therapy. Raw carrots, by stimulating the intestine, often help to lower estrogen and increase progesterone. One of the thyroid hormone's important functions is to improve digestion and bowel health.

Rheumatoid arthritis, osteoarthritis, lupus, scleroderma, and a variety of other "autoimmune" diseases and connective tissue diseases respond well to these hormonal treatments.

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19
THE CERVICAL CANCER SCARE AND OTHER APPROACHES TO CANCER

Many women with abnormal Pap smears, even with a biopsy showing the so-called "carcinoma in situ," have returned to normal in just two months with a diet including the following: 90 grams of protein, 500 mg. of magnesium as chloride, 100,000 units of vitamin A, 400 units of vitamin E, 5 mg. folic acid, 100 mg. pantothenic acid, 100 mg. of B_6 and niacinamide, and 500 mg. of vitamin C, with progesterone and thyroid as needed. Liver should be eaten once a week, because of its high B-vitamin content. Some of the women apply vitamin A (not carotene) directly to the cervix.

Estrogen is known to cause uterine cancer, but the pervasive marketing of estrogen led to solving that problem by the mass removal of American uteruses. The evidence is clear, however, that many tissues have estrogen receptors, and can be cancerized by exposure to estrogen. Breast, lung, brain, and liver are coming to be widely recognized as sites of estrogen-induced cancers in humans, 50 years after Lipschutz demonstrated the extensive nature of estrogen carcinogenesis in animals. The pancreas, which has estrogen receptors, is another organ that I believe is significantly cancerized by estrogen.

Progesterone's anti-estrogen effect has been successfully used to treat some uterine and breast cancers, but the doses were never high enough to duplicate the levels that exist in late pregnancy. I believe it is irrational to use less than the maximum physiological level, in attempting to reverse a condition which resulted from years of severe deficiency. When progesterone dissolved in benzyl alcohol with sesame oil is injected, progesterone crystals are deposited, inertly, in the tissue. Even this limited approach has produced some visible results.

I believe the fact that the cancer death rate keeps rising disproves the claim that there has been progress in the cure of cancer. Everyone over 50 contains some tissue that can be diagnosed as cancer. Though not everyone dies from cancer, it could be diagnosed in everyone, if a sufficient diagnostic effort were made. Then, 75% of "all cancers" could be "cured," though just as many people would die from it. The cancer situation is so thoroughly unscientific that I am not convinced that it is worthwhile to make any effort to diagnose cancer. At a cancer

conference, a very high proportion of the male physicians, when asked what they would do if they had prostate cancer, said they would do nothing; that response seems to be justified by the evidence accumulated for several decades, that treatment for prostate cancer hasn't clearly prolonged life. More aggressive diagnosis will certainly improve the "cure rate," but until the population's death rate from prostate cancer decreases, it is hard to have confidence in therapies based on fundamentally confused notions of the biology of cancer. If something harms your vitality, and is just as toxic to your immune system, your liver, and your brain, as it is to cancer cells, the medical situation seems analogous to that of the army that destroys a town to save it.

Benign breast disease, breast cancer and pre-cancerous conditions have been found to be associated with a progesterone deficiency and excess estrogen.(1) Some additional references are given in *Nutrition for Women.* Since progesterone deficiency and excess estrogen can be caused by either a thyroid deficiency or a protein deficiency, the most important cause of the steroid imbalance, and of the hormone related cancers, is hypothyroidism. Broda Barnes has discussed this issue in his books. (Protein deficiency is one cause of hypothyroidism.) Vitamin A, vitamin E, and thyroid have all been used effectively to relieve benign breast disease. Caffeine actually has been repeatedly shown to protect against cancer. Minton's so-called study which led to a generalized fear of coffee as a cause of breast disease was based on confused reasoning. I believe anti-inflammatory drugs such as aspirin or prostaglandin inhibitors such as indomethacin have a rational place in cancer therapy, especially if (like aspirin) they have some antihistamine activity. (The prostaglandins have now been implicated in all of the major types of cancer.) Estrogen tends to be deposited in inflamed tissues, and in that sense those drugs might be considered as part of an anti-estrogenic program.

Simple derivatives of glucose, glucuronic acid and glucaric acid, have been proposed as substances that might limit the deposition of estrogen in inflamed tissues. Recent studies using glucarate and various forms of vitamin A have produced good effects in breast cancer.

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20
WARBURG'S CANCER THEORY, CACHEXIA AND THYROID THERAPY

Otto Warburg[1] demonstrated that all cancers have defective respiration, by which he meant that glucose is consumed too rapidly, even when there is adequate oxygen. The excessive consumption of glucose in the presence of oxygen is called aerobic glycolysis, and is typical of cancer. Oxygen may be consumed, but it does not result in the production of sufficient ATP to inhibit glycolysis (by the Pasteur effect). This generally means that excess lactate will be produced and will leave the cell, will be detected by other tissues, and will be processed by the liver into glucose. Lactate is a sufficient stimulus to trigger the stress reaction, and in many people causes an anxiety syndrome. Since resynthesis of glucose from lactate by the liver requires much more energy than is derived from conversion of glucose to lactate, the tumor's formation of lactate constitutes a large burden to the organism. Total energy consumption would increase, because of intense but inefficient metabolism in the tumor and in the liver, and also possibly because of stress-induced brain excitation and the catabolism of muscle and other tissue proteins. Cortisol elevates blood glucose and would inhibit the thyroid. Since there is evidence of thyroid deficiency in various cancers, and since thyroid supplementation reduces the incidence of spontaneous or induced tumors in animal studies, thyroid therapy would be desirable in cancer, especially if there is cachexia. Gerson,[2] Tallberg,[3] and others have reported good results from using thyroid as part of supportive therapy.

The stereotype of the hypothyroid person as over-weight will lead the typical physician to believe that metabolic stimulation by thyroid would be exactly the opposite of what the cachectic patient needs. The relevant effects of thyroid (especially with progesterone, to promote tissue response to thyroid, to block cortisol production, and to provide general anti-stress physiological support) however, are stimulation of protein synthesis and the prevention of lactate formation--or the stimulation of its oxidation, either by the tumor itself or by other tissues, to prevent its entry into the Cori cycle, for gluconeogenesis. Cachexia strumipriva, the wasting disease that used to result following removal of the thyroid gland when the thyroid hormone wasn't replaced, should be

kept in mind, since it is a situation in which thyroid cures cachexia, stimulating anabolic processes.

There has been publicity in recent decades about various substances produced by cancers that induce the growth of blood vessels, providing the tumors with the circulation needed for growth. Since lactic acid is an adequate stimulus for such growth, and is produced by tumors, it is remarkable that it has been so consistently ignored as a reasonable point of intervention for limiting tumor growth. Thyroid and magnesium make respiration efficient, in the sense of producing ATP, which is required for the Pasteur effect to turn off glycolysis. Lactic acid can't be made (in humans) from fats or alcohol, a point which is often overlooked by biochemists who work with bacteria, and so the use of acetic acid, butyric acid, and other fatty acids (as in coconut oil, for example), combined with adequate thyroid hormone and magnesium, should make a significant contribution toward removing the lactate stimulus for increased blood supply to the tumor. The carbon dioxide produced by the action of thyroid is itself involved in the suppression of lactic acid formation.

Progesterone and pregnenolone, by reducing the cancer-induced excess of the glucocorticoid hormones, would also make a contribution to decreasing the supply of glucose to the tumor.

Warburg believed that a riboflavin deficiency was an important contributor to the development of defective respiration, but he also pointed out that the simple lack of oxygen would promote the development of cancer. I have emphasized the role of estrogen in creating an oxygen deficiency. Since it inhibits the secretion of thyroxin at the glandular level, and antagonizes thyroxin at the cellular level, estrogen is a good candidate for the main cause of the respiratory defect. It also antagonizes other respiratory factors, such as magnesium and vitamin E, and excess estrogen actually impedes oxygenation of the blood. (Both low thyroid and high estrogen are known to cause an emphysema-like interference with diffusion of oxygen into the lung capillaries.)

Radioactive estrogen has been shown to accumulate selectively in (liver) cancer cells, which is remarkable since that behavior is so untypical of liver cells. One of my first research projects had to do with the fact that estrogen promotes the formation of beta-glucuronidase, an enzyme which can reverse the reaction which normally occurs in the liver, detoxifying estrogen by combining it with glucuronic acid. Irritated tissues, and all cancers, contain beta-glucuronidase, with the capacity to

're-toxify" estrogen in the irritated or cancerous site, depositing it locally and negating the liver's protective function. More recently, breast cancer cells have been found to contain sulfatase enzymes, with the same kind of function, since the liver's other main route of estrogen detoxication is by combining it with sulfate. A systematic anti-estrogen program (including adequate protein to sustain liver function) would help to minimize the cancer-promoting action of this locally deposited estrogen. I think of the appearance of these estrogen-releasing enzymes in irritated tissue as part of a system for promoting regeneration. In the uterus, estrogen promotes simple growth, and progesterone promotes differentiation. I think something analogous happens in other tissues, with a variety of substances supporting differentiation.

Once we accept Warburg's thesis, that damaged respiration is the prime cause of cancer, the therapeutic use of thyroid in cancer seems obvious. Aging and estrogen-dominance are other states in which cells seem to be relatively insensitive to thyroid hormones. (Unsaturated fats are involved in resistance to thyroid, and promote the incidence of cancer in a variety of ways.) If the liver is a main site of T_4's conversion to T_3, cancer patients may require very large doses of thyroid hormone, or else direct use of T_3 (possibly in large doses), since the liver is so likely to be inefficient. Incidentally, thyroid's ability to improve digestion and peristalsis is important for liver function; endotoxin absorbed from the intestine can be a serious burden to the liver, and it is known to cause a large increase in the blood estrogen level.

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21
MIGRAINE, VARICOSE VEINS, EPILEPSY

This group of problems relates to the behavior of the muscles in the walls of blood vessels. Estrogen tends to decrease the muscle tone in veins, while increasing it (especially if adrenalin is present) in arteries, and progesterone increases the tone of veins. One aspect of estrogen's production of increased problems with blood clots is that it slows circulation, allowing clots to form in the slow moving blood of the large veins, especially in the legs.

The times (premenstrually, in pregnancy, around menopause, in hypothyroidism, for example) when estrogen is high and progesterone is low, are the times of increased incidence of migraines, epileptic seizures, and development of varicose veins.

There is increasing recognition that progesterone can cure migraines and epilepsy, but there is a mechanistic dogma about varicose veins, largely based on a strange idea that has been perpetuated by medical schools that veins "don't have muscular walls." Believing that veins don't have muscles, many physicians can't conceive of any way in which an enlarged vein could correct itself: "The valves are defective." But when they have enough progesterone in relation to estrogen, the walls contract, narrowing the channel so the valves are able to function. Visible veins around the ankles often disappear, even in older people, when the hormone balance is improved.

Since migraine and epilepsy can be debilitating, I always urge people to use progesterone to get rid of their symptoms, so they can focus on correcting the basic metabolic problems, which usually relate to diet and thyroid function.

A quick demonstration of progesterone's effect on the veins can be done by holding the hands at waist level. If the veins on the back of the hand bulge visibly, an appropriate oral dose of progesterone will regulate the tone of the smooth muscles in the veins, causing them to contract and become relatively invisible within a few minutes. Once, I watched a woman whose hands were disfigured by gnarled purple blood vessels, who took about 30 mg. of progesterone every 10 minutes. After the fifth dose, her hands suddenly (in a moment when we weren't watching them closely) were transformed into perfectly beautiful young hands. Progesterone's effects can be similarly quick in migraine and epilepsy.

22
NERVES

Almost everyone knows that estrogen causes water retention and edema, but few people seem to be aware that the edema associated with either high estrogen or low thyroid (which go together so closely) involves the retention of water without a sufficient amount of sodium to balance it--the edema is "hypotonic." This means that the water in the blood in effect forces itself into cells and connective tissues, causing them to swell. Some cells aren't damaged very much by a little swelling, but when cells are enclosed by a rigid container of bone or connective tissue, the pressure will tend to prevent the entry of blood, and will cause structural changes, simply because the contents are too big for the container.

The carpal tunnel syndrome involves the pinching of nerves by ligaments in the wrist, damaging their function. The spinal cord and brain are enclosed, and extreme swelling can cut off the blood supply, causing death. Before that point is reached, swelling can cause a great variety of nervous symptoms.

Swelling of the lower spinal cord can cause weakness or paralysis of the legs, or various sensory or circulatory problems. Veterinarians have recognized conditions in dogs and horses caused by spinal swelling (and in dogs the problem was traced to hypothyroidism), but analogous symptoms in people are often ascribed to the mysterious "multiple sclerosis."

Multiple sclerosis is strongly associated with hormone imbalances, and disproportionately affects women in their reproductive years. Progesterone and thyroid are crucial for maintaining and repairing the myelin sheath that deteriorates in MS. Blood clots are known to be associated with the "plaques" in the brain, and a low protein diet predisposes to abnormal clotting, partly through its effect on the balance of estrogen and the anti-estrogens. One of the first people I knew who used progesterone was a woman who had cured her multiple sclerosis/optic neuritis with progesterone. Often, thyroid supplementation by itself eliminates the symptoms of MS.

Since the edema of estrogen excess and thyroid deficiency is hypotonic, eating extra salt is appropriate, but the body can't retain the salt unless the hormone balance is corrected.

23
ALZHEIMER'S DISEASE

The results seen in several Alzheimer's studies could have a significance larger than what has been suggested by the investigators. A diagnostic bias has been reported to result from the use of standardized tests based on vocabulary, because education increases vocabulary, and tends to cover up the loss of vocabulary that occurs in dementia. In the Framingham study, it was concluded that there was a real association of lower educational level with dementia, but the suggestion was made that self-destructive practices such as smoking were more common among the less educated.

The Seattle study of the patients in a health maintenance organization showed a very distinct difference in educational level between the demented and the non-demented, both of whom had roughly similar frequency of prescriptions for estrogen. The features that seemed important to me, that weren't discussed by the authors, were that the demented women had a much lower rate of progestogen use, and a much higher incidence of hysterectomy, which interferes with natural progesterone production.

Although Brenner, et al., in the Seattle study concluded that "this study provides no evidence that estrogen replacement therapy has an effect on the risk of Alzheimer's disease in postmenopausal women," they reported that "Current estrogen use of both the oral and the vaginal routes had odds ratios below 1, while former use of both types yielded odds ratios above 1...." (They seem to neglect the fact that Alzheimer's-type disease in old people has a long developmental history, so it is precisely the "former" use that is relevent. 31% of the demented women had formerly used estrogen, and only 20% of the control group. Since estrogen is a brain excitant, present use creates exactly the same sort of effect on verbal fluency and other signs of awareness of the environment that a little cocaine does. Anyone who neglects this effect is probably deliberately constructing a propaganda study.) This observation, that the demented had 155% as much *former* estrogen use as the normal group, as well as the difference in rates of progestogen use (normal patients had 50% more progestogen use than demented) and hysterectomy (demented had 44.1% vs. 17% in the normals, i.e., 259% as many; the incidence of hysterectomies after the age of 55, *which is a strong indication of a natural excess of estrogen, in the demented was*

374% of the incidence in the non-demented), should call for a larger study to clarify these observatons, which tend to indicate that exposure to estrogen in middle-age increases the risk of Alzheimer's disease in old age, and that even medical progestogens offer some protection against it.

(Although this study might have been bigger and better, it is far better than the junk-studies that have been promoted by the pharmaceutical publicity machine. I have seen or heard roughly 100 mentions of the pro-estrogen anti-scientific "studies," and none mentioning this one.)

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24
ECLAMPSIA IN THE REAL ORGANISM: A Paradigm of General Distress Applicable to Infants, Adults, Etc.

To prevent the appropriation and abuse of our language by academic and professional cliques, I like to recall my grandparents' speech. When my grandmother spoke of eclampsia, the word was still normal English, that reflected the Greek root meaning, "shining out," referring to the visual effects that are often prodromal to seizures. The word was most often used in relation to pregnancy, but it could also be applied to similar seizures in young children. The word is the sort that might have been coined by a person who had experienced the condition, but the experience of seeing hallucinatory lights is seldom mentioned in the professional discussion of "eclampsia and preeclampsia."

Metaphoric thinking--using comparisons, models, or examples--is our natural way of gaining new understanding. Ordinary language, and culture, grow when insightful comparisons are generally adopted, extending the meaning of old categories. Although the free growth of insight and understanding might be the basic law of language and culture, we have no institutions that are amenable to that principle of free development of understanding. Institutions devoted to power and control are naturally hostile to the free development of ideas.

Among physicians, toxemia (meaning poisons in the blood) has been used synonymously with preeclampsia, to refer to the syndrome in pregnant women of high blood pressure, albumin in the urine, and edema, sometimes ending in convulsions. Eclampsia is reserved for the convulsions themselves, and is restricted to the convulsions which follow preeclampsia, when there is "no other reason" for the seizure such as "epilepsy" or cerebral hemorrhage. Sometimes it is momentarily convenient to use medical terms, but we should never forget the quantity of outrageous ignorance that is attached to so many technical words when they suggest the identity of unlike things, and when they partition and isolate things which have meaning only as part of a process. Misleading terminology has certainly played an important role in retarding the understanding of the problems of pregnancy.

In 1974, when I decided to write Nutrition for Women, I was motivated by the awful treatment I saw women receiving, especially

during pregnancy, from physicians and dietitians. Despite the research of people like the Shutes and the Biskinds, there were still "educated" and influential people who said that the mother's diet had no influence on the baby. (That strange attitude affects many aspects of behavior and opinion.)

How can people believe that the mother's diet has no effect on the baby's health? Textbooks used to talk about the "insulated" fetus, which would get sufficient nutrients from the mother's body even if she were starving. To "prove" the doctrine, it was pointed out that the fetus gets enough iron to make blood even when the mother is anemic. In the last few years, the recognition that smoking, drinking, and using other drugs can harm the baby has helped to break down the doctrine of "insulation," but there is still not a medical culture in which the effects of diet on the physiology of pregnancy are appreciated. This is because of a mistaken idea about the nature of the organism and its development. "Genes make the organism," according to this doctrine, and if there are congenital defects in the baby, the genes are responsible. A simple sort of causality flows from the genes to the finished organism, according to that idea. **It was taught that if "the genes" are really bad, the defective baby can make the mother sick, and she contributed to the baby's bad genes.** The idea isn't completely illogical, but it isn't based on reality, and it is demonstrably false. (Race, age and parity have no effect on incidence of cerebral palsy; low birth weight and complications of pregnancy are associated with it: J. F. Eastman, "Obstetrical background of 753 cases of cerebral palsy," Obstet. Gynecol. Surv. 17, 459-497, 1962.)

Although Sigmund Freud sensibly argued in 1897 that it was more reasonable to think that an infant's cerebral palsy was caused by the same factors that caused the mother's sickness, than to think that the baby's cerebral palsy *caused* maternal sickness and premature labor, **more than 50 years later people were still taking seriously the idea that cerebral palsy might cause maternal complications and prematurity.** (A.M. Lilienfield and E. Parkhurst, "A study of the association of factors of pregnancy and parturition with the development of cerebral palsy," *Am. J. Hyg. 53*, 262-282, 1951.)

Medical textbooks and articles still commonly list the conditions that are associated with eclampsia: Very young and very old mothers, a first pregnancy or a great number of previous pregnancies, diabetes, twins, obesity, excessive weight gain, and kidney disease. Some authors, observing the high incidence of eclampsia in the deep South, among

Blacks and on American Indian reservations, have suggested that it is a genetic disease because it "runs in families." If poverty and malnutrition are also seen to "run in families," some of these authors have argued that the bad genes which cause birth defects also cause eclampsia and poverty. (L. C. Chesley, et al., "The familial factor in toxemia of pregnancy," Obstet. Gynec. 32, 303-311, 1968, reported that women whose mothers suffered eclampsia during their gestation were likely to have eclampsia themselves. Some "researchers" have concluded that eclampsia is good, because many of the babies die, eliminating the "genes" for eclampsia and poverty.)* Any sensible farmer knows that pregnant animals must have good food if they are to successfully bear healthy young, but of course those farmers don't have a sophisticated knowledge of genetics.

The inclusion of obesity and "excessive weight gain" among the conditions associated with eclampsia has distracted most physicians from the fact that malnutrition is the basic cause of eclampsia. The pathologist who, knowing nothing about a woman's diet, writes in his autopsy report that the subject is "a well nourished" pregnant woman, reflects a medical culture which chooses to reduce "nutritional adequacy" to a matter of gross body weight. The attempt to restrict weight gain in pregnancy has expanded the problem of eclampsia beyond its association with poverty, into the more affluent classes.

Freud wasn't the first physician who grasped the idea that the baby's health depends on the mother's, and that her health depends on good nutrition. Between 1834 and 1843, John C. W. Lever, M.D., discovered that 9 out of 10 eclamptic women had protein in their urine. He described an eclamptic woman who bore a premature, low-weight baby, as having "...been living in a state of most abject penury for two or three months, subsisting for days on a single meal of bread and tea. Her face and body were covered with cachectic sores." ("Cases of puerperal convulsions," *Guy's Hospital Reports, Volume 1, series 2,* 495-517, 1843.) S. S. Rosenstein observed that eclampsia was preceded by changes in the serum (*Traite Pratique des Maladies des Reins,* Paris, 1874). L. A. A. Charpentier specifically documented low serum albumin as a cause of eclampsia (*A Practical Treatise on Obstetrics, Volume 2,* William Wood & Co., 1887). Robert Ross, M.D., documented the role of malnutrition as the cause of proteinuria and eclampsia (*Southern Medical Journal 28,* 120, 1935).

In outline, we can visualize a chain of causality beginning with a diet deficient in protein, impairing liver function, producing inability to

store glycogen, to inactivate estrogen and insulin, and to activate thyroid. Low protein and high estrogen cause increased tendency of the blood to clot. High estrogen destroys the liver's ability to produce albumin (G. Belasco and G. Braverman, *Control of Messenger RNA Stability*, Academic Press, 1994). Low thyroid causes sodium to be lost. The loss of sodium albuminate causes tissue edema, while the blood volume is decreased. Decreased blood volume and hemoconcentration (red cells form a larger fraction of the blood) impair the circulation. Blood pressure increases. Blood sugar becomes unstable, cortisol rises, increasing the likelihood of premature labor. High estrogen, hypoglycemia, viscous blood, increased tendency of the blood to clot cause seizures. Women who die from eclampsia often have extensive intravascular clotting, and sometimes the brain and liver show evidence of earlier damage, probably from clots that have been cleared. (Sometimes prolonged clotting consumes fibrinogen, causing inability to clot, and a tendency to hemorrhage.) *M. M. Singh, "Carbohydrate metabolism in pre-eclampsia," Br. J. Obstet. Gynaecol. 83, 124-131. 1976. Sodium decrease, R. L. Searcy, Diagnostic Biochemistry, McGraw-Hill, 1969. Viscosity, L. C. Chesley, 'Hypertensive Disorders in Pregnancy, Appleton-Century-Crofts, 1978. Clotting, T. Chatterjee, et al., "Studies on plasma fibrinogen level in preeclampsia and eclampsia, Experientia 34, 562-3, 1978; D. M. Haynes, "Medical Complications During Pregnancy, McGraw-Hill Co. Blakiston Div., 1969. Progesterone decrease, G. V. Smith, et al., "Estrogen and progestin metabolism in pregnant women, with especial reference to pre-eclamptic toxemia and the effect of hormone administration," Am. J. Obstet. Gynecol. 39, 405, 1940; R. L. Searcy, Diagnostic Biochemistry, McGraw-Hill, 1969.*

But the simple chain of causality has many lines of feedback, exacerbating the problem, and the nutritional problem is usually worse than a simple protein deficiency. B vitamin deficiencies alone are enough to cause the liver's underactivity, and to cause estrogen dominance, and a simple vitamin A deficiency causes an inability to use protein efficiently or to make progesterone, and in itself mimics some of the effects of estrogen.

The clotting which sometimes kills women, can, if it is not so extensive, cause spotty brain damage, similar to that seen in "multiple sclerosis," or it can occur in the liver, or other organ, or in the placenta, or in the fetus, especially in its brain and liver. Some cases of supposed "post-partum psychosis" have been the result of multiple strokes. When large clots occur in the liver or placenta, the fibrinogen which has been

providing the fibrin for disseminated intravascular coagulation can appear to be consumed faster than it is produced by the liver. I think its disappearance may sometimes be the result of the liver's diminished blood supply, rather than the "consumption" which is the way this situation is usually explained. It is at this point that hemorrhages, rather than clots, become the problem. The undernourished liver can produce seizures in a variety of ways--clots, hemorrhages, hypoglycemia, and brain edema, for example, so eclampsia needn't be so carefully discriminated from "the other causes of seizures."

Because I had migraines as a child, I was interested in their cause. Eating certain foods, or skipping meals, seemed to be involved, but I noticed that women often had migraines premenstrually. Epilepsy too, I learned, often occurred premenstrually.

In my experience of migraine, nausea and pain followed the visual signs, which consisted of a variable progression of blind spots and lights. When I eventually learned that I could stop the progression of symptoms by quickly eating a quart of ice cream, I saw that my insight could be applied to other situations in which similar visual events played a role, especially "eclampsia" and "epilepsy." For example, a woman who was 6 months pregnant called me around 10 o'clock one morning, to say that she had gone blind, and was alone in her country house. She said she had just eaten breakfast around 9 AM, and wasn't hungry, but I knew that the 6 month fetus has a great need for glucose, so I urged her to eat some fruit. She called me 15 minutes later to report that she had eaten a banana, and her vision had returned.

Early in pregnancy, "morning sickness" is a common problem, and it is seldom thought to have anything to do with eclampsia, because of the traditional medical idea that the fetus "causes" eclampsia, and in the first couple of months of pregnancy the conceptus is very small. But salty carbohydrate (soda crackers, typically) is the standard remedy for morning sickness. Some women have "morning sickness" premenstrually, and it (like the nausea of migraine) is eased by salt and carbohydrate. X-ray studies have demonstrated that there are spasms of the small intestine (near the bile duct) associated with estrogen-induced nausea.

Hypoglycemia is just one of the problems that develops when the liver malfunctions, but it is so important that orange juice or Coca Cola or ice cream can provide tremendous relief from symptoms. Sodium (orange juice and Pepsi provide some) helps to absorb the sugar, and--more basically--is essential for helping to restore the blood volume. Pepsi has been recommened by the World Health Organization for the

rehydration of babies with diarrhea, in whom hypovolemia (thickening of the blood from loss of water) is also a problem.

The problem of refeeding starving people has many features in common with the problem of correcting the liver malfunction and hormone imbalances which follow prolonged malnutrition of a milder sort. The use of the highest quality protein (egg yolk or potato juice, or at least milk or meat) is important, but the supplementation of thyroid containing T_3 is often necessary. Intravenous albumin, hypertonic solutions of glucose and sodium, and magnesium in an effective form should be helpful (magnesium sulfate injected intramuscularly is the traditional treatment for eclampsia, since it is quickly effective in stopping convulsions). While the sodium helps to restore blood volume and to regulate glucose, under some circumstances (high aldosterone) it helps to retain magnesium; aldosterone is not necessarily high during eclampsia.. Triiodothyronine directly promotes cellular absorption of magnesium. Hypertonic glucose with minerals is known to decrease the destruction of protein during stress: M. Jeevanandam, et al., *Metabolism 40,* 1199-1206, 1991.

Katherina Dalton observed that her patients who suffered from PMS (and were benefitted by progesterone treatment) were likely to develop "toxemia" when they became pregnant, and to have problems at the time of menopause. In these women, it is common for "menstruation" to continue on the normal cycle during the first several months of pregnancy. This cyclic bleeding seems to represent times of an increased ratio of estrogen to progesterone, and during such periods of cyclic bleeding the risk of miscarriage is high. Researchers found that a single injection of progesterone could sometimes eliminate the signs of toxemia for the remainder of the pregnancy. Katherina Dalton, who continued to give her patients progesterone throughout pregnancy, later learned that the babies treated in this way were remarkably healthy and bright, while the average baby delivered after a "toxemic" pregnancy has an IQ of only 85.

Marian Diamond's work with rats clearly showed that increased exposure to estrogen during pregnancy reduced the size of the cerebral cortex and the animals' ability to learn, while progesterone increased the brain size and intelligence. Zamenhof's studies suggested that these hormones probably have their effects largely through their actions on glucose, though they also affect the availability of oxygen in the same way, and have a variety of direct effects on brain cells that would operate toward the same end.

If Katherina Dalton's patients' IQs averaged 130, instead of the expected 85, the potential social effects of proper health care during pregnancy are enormous.

But there is evidence that healthy gestation affects more than just the IQ. Strength of character, ability to reason abstractly, and the absence of physical defects, for example, are strongly associated with weight at birth.

Government studies and Social Security statistics suggest the size of the problem. The National Institute of Neurological Diseases and Stroke found that birth weight was directly related to IQ at age four, and that up to half of all children who were underweight at birth have an IQ under 70.(Chase.) According to standard definitions, about 8% of babies in the U.S. have low birth weight.

Among people receiving Social Security income because of disability that existed at the age of 18, 75% were disabled before birth. In 94% of these cases, the abnormally was neurological. (HEW.)
A study of 8 to 10-year-old children found that abstract verbal reasoning and perceptual/motor integration are more closely related to birth weight than they are to IQ. (Wiener.)

National nutritional data show that in the U.S. **the development of at least a million babies a year is "substantially compromised" by prenatal malnutrition.** Miscarriages, which are also causally related to poor nutrition, occur at a rate of a few hundred thousand per year. (Williams.)

When a muscle is fatigued, it swells, taking up sodium and water, and it is likely to become sore. Energy depletion causes any cell to take up water and sodium, and to lose potassium. An abnormal excess of potassium in the blood, especially when sodium is low, affects nerve, muscle, and secretory cells; a high level of potassium can stop the heart, for example. Cellular energy can be depleted by a combination of work, insufficient food or oxygen, or a deficiency of the hormones needed for energy production. When the swelling happens suddenly, the movement of water and sodium from the blood plasma into cells decreases the volume of blood, while the quantity of red cells remains the same, making the blood more viscous.

During the night, as adrenalin, cortisol, and other stress hormones rise, our blood becomes more viscous and clots more easily. In rats, it has been found that the concentration of serum proteins increases significantly during the night, presumably because water is moving out of

the circulatory system. Even moderate stress causes some loss of water from the blood.

If a person is malnourished, a moderate stress can overcome the body's regulatory capacity. If tissue damage is extreme, or blood loss is great, even a healthy person experiences hypovolemia and shock.
C.A. Crenshaw, who was a member of the trauma team at Parkland Hospital in Dallas that worked on Kennedy and Oswald, had been involved in research with G. T. Shires on traumatic shock. In his words, "we made medical history by discovering that death from hemorrhagic shock (blood loss) can be due primarily to the body's adjunctive depletion of internal salt water into the cells." (Shires' work involved isotopes of sodium to show that sodium seems to be taken up by cells during shock.)

According to Crenshaw, "Oswald did not die from damaged internal organs. He died from the chemical imbalances of hemorrhagic shock. From the time he was shot...until the moment fluids were introduced into the body..." [19 minutes] "there was very little blood circulating in Oswald's body. As a result, he was not getting oxygen, and waste built up in his cells. Then, when the fluids were started, the collection of waste from the cells was dumped into the bloodstream, suddenly increasing the acid level, and delivering these impurities to his heart. When the contaminated blood reached the heart, it went into arrest...." The "waste" he refers to includes potassium and lactic acid. Crenshaw advocates the use of Ringer's lactate to replace some of the lost fluid. Since the blood already contains a large amount of lactate because the body is unable to consume it, this doesn't seem reasonable. I think a hypertonic version of Locke's solution, containing glucose and sodium bicarbonate as well as sodium chloride, would be better, though I think the potassium should be omitted too, and extra magnesium would seem desirable. Triiodothyronine, I suspect, would help tremendously to deal with the problems of shock, causing potassium, magnesium, and phosphate to move back into cells, and sodium to move out, helping to restore blood volume and reduce the wasteful conversion of glucose to lactic acid.

Albumin has been used therapeutically in preeclampsia (Kelman), to restore blood volume. Synthetic polymers with similar osmotic properties are sometimes used in shock, and might also be useful in eclampsia, but simply eating extra protein quickly restores blood albumin. For example, in a group of women who were in their seventh month of pregnancy, the normal women's serum osmotic pressure was 247 mm. of water, that of the women with nonconvulsive toxemia was 215 mm., and

in the women with eclampsia, the albumin and osmotic pressure were lowest, with a pressure of 175 mm. In the eighth month, the toxemic women who ate 260 grams of protein daily had a 7% increase in osmotic pressure, and a group who ate 20 grams had a decline of 9%.(Strauss) In a group of preeclamptics, plasma volume was 39% below that of normal pregnant women.

Besides protein deficiency and other nutritional deficiencies, excess estrogen and low thyroid can also limit the liver's ability to produce albumin. Hypovolemia reduces liver function, and (like hepatic infarcts) will reduce its ability to maintain albumin production..

The studies which have found that hospitalized patients with the lowest albumin are the least likely to survive suggest that the hypovolemia resulting from hepatic inefficiency is a problem of general importance, and that it probably relates to the multiple organ failure which is an extremely common form of death among hospitalized patients. A diet low in sodium and protein probably kills many more people than has been documented. If old age is commonly a hypovolemic condition, then the common salt restriction for old-age hypertension is just as irrational as is salt-restriction in pregnancy or in shock. Thyroid (T_3), glucose, sodium, magnesium and protein should be considered in any state in which weakened homeostatic control of the composition of plasma is evident.

***Note:** Although Konrad Lorenz (who later received the Nobel Prize) was the architect of the Nazi's policy of "racial hygiene" (extermination of those with unwanted physical, cultural, or political traits which were supposedly determined by "genes") he took his ideas from the leading U.S. geneticists, whose works were published in the main genetics journals. Following the Nazi's defeat, some of these journals were renamed, and the materials on eugenics were often removed from libraries, so that a new historical resume could be presented by the profession.

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25
ESTRIOL, DES, DDT, ETC.

As the result of industrial promotion, including product advertising and grants for research, "weak estrogens" and "antioxidants" derived from soy are being discussed as means to prevent breast and prostate cancer, heart disease, stress and aging.

Japanese women used to be very free of breast cancer, and when their children grew up in the U.S., their incidence of the disease was like that of Americans. How odd that the soybean should be singled out for responsibility. Japanese breast cancer incidence has risen sharply in recent years. Did they stop eating tofu? Did their traditional use of seaweed as food have nothing to do with their health? Did the traditional home-bound isolation of Japanese women, their avoidance of smoking and drinking, have no effect on hormones and cancer? Their calorie intake? Iodine and trace minerals? What types of protein and fat, in what quantities, did they use?

Another so-called weak estrogen, estriol, is being promoted by drug companies for the "alternative medical" market, with the circulation of an editorial from JAMA, recommending it for preventing breast cancer. A review of the use of estrogens reported in JAMA (only up to 1987) found nearly 200 different "indications" for its use. (Palmlund, 1996.) Using the conservative language of that journal, such use could be said to constitute wildly irresponsible "empirical" medical practice. More appropriate language could be used.

Pollution of the environment and food supply by estrogenic chemicals is getting increased attention. Early in the study of estrogens, it was noticed that soot, containing polycyclic aromatic hydrocarbons, was both estrogenic and carcinogenic. Since then, it has been found that phenolics and chlorinated hydrocarbons are significantly estrogenic, and that many estrogenic herbicides, pesticides, and industrial by-products persist in the environment, causing infertility, deformed reproductive organs, tumors, and other biological defects, including immunodeficiency. In the Columbia River, a recent study found that about 25% of the otters and muskrats were anatomically deformed.

Estrogenic pollution kills birds, panthers, alligators, old men, young women, fish, seals, babies, and ecosystems. Some of these chemicals are sprayed on forests by the US Department of Agriculture,

where they enter lakes, underwater aquifers, rivers, and oceans. Private businesses spray them on farms and orchards, or put them into the air as smoke or vapors, or dump them directly into rivers. Homeowners put them on their lawns and gardens.

Natural estrogens, from human urine, enter the rivers from sewage. Many tons of synthetic and pharmaceutical estrogens, administered to menopausal women in quantities much larger than their bodies ever produced metabolically, are being added to the rivers.

In the same way that weak estrogens in the environment may become hundreds of times more estrogenic by synergistic interactions (J. A. McLachlan, et al., *Science,* June 7, 1996), combinations of natural, medical, dietary, and environmental estrogens are almost certain to have unexpected results. The concept of a "protective estrogen" is very similar to the idea of "protective mutagens" or "protective carcinogens," though *in the case of estrogens, their promoters don't even know what the normal, natural functions of estrogen are.*

In November, 1995, an international conference was held to study the problem of "Environmental endocrine-disrupting chemicals," and to devise strategies for increasing public awareness of the seriousness of the problem. Their "Statement from the work session" says "New evidence is especially worrisome because it underscores the exquisite sensitivity of the developing nervous system to chemical perturbations that result in functional abnormalities." "This work session was convened because of the growing concern that failure to confront the problem could have major economic and societal implications." **"We are certain of the following: Endocrine-disrupting chemicals can undermine neurological and behavioral development and subsequent potential of individuals...."** "Because the endocrine system is sensitive to perturbation, it is a likely target for disturbance." "Man-made endocrine-disrupting chemicals range across all continents and oceans. They are found in native populations from the Arctic to the tropics, and, because of their persistence in the body, can be passed from generation to generation." **"...many endocrine-disrupting contaminants, even if less potent than the natural products, are present in living tissue at concentrations millions of times higher than the natural hormones."** "The developing brain exhibits specific and often narrow windows during which exposure to endocrine disruptors can produce permanent changes in its structure and function."

In spite of this increased exposure to estrogens, there is a new wave of advertising of estrogenic substances, based on the idea that weak

estrogens will provide protection against strong estrogens. The environmental background of estrogenic pollution already provides a continuous estrogenic exposure. In the 1940s, Alexander Lipshuts demonstrated that a continuous, weak estrogenic stimulus was immensely effective in producing, first fibromas, then cancer, in one organ after another, and the effect was not limited to the reproductive system. How is it possible that the idea of "protection" from a weak estrogen seems convincing to so many? Isn't this the same process that we saw when the nuclear industry promoted Luckey's doctrine of "radiation hormesis," literally the claim that "a little radiation is positively good for us"?

DES (diethyl stilbestrol) is one of the most notorious estrogens, because studies in humans revealed that its use during pregnancy not only caused cancer, miscarriages, blood clots, etc., in the women who used it, but also caused cancer, infertility, and deformities in their children, and even in their grandchildren. (But those transgenerational effects are not unique to it.)

Besides the absurd use of DES to prevent miscarriages, around 1950 it was also used to treat vulvovaginitis in little girls, for menstrual irregularity at puberty, to treat sterility, dysfunctional bleeding, endometriosis, amenorrhea, oligomenorrhea, dysmenorrhea, migraine headaches, nausea and vomiting, and painful breast engorgement or severe bleeding after childbirth.

DES is a "weak" estrogen, in the sense that it doesn't compete with natural estrogens for the "estrogen receptors." (Estriol binds more strongly to receptors than DES does: "Cytosolic and nuclear estrogen receptors in the genital tract of the rhesus monkey," *J. Steroid Bioch. 8(2)*, 151-155, 1977.) Pills formerly contained from 5 to 250 mg. of DES. The 1984 *PDR* lists doses for hypogonadism and ovarian failure as 0.2 to 0.5 mg. daily. In general, dosage of estrogens decreased by a factor of 100 after the 1960s.

An aggressively stupid editorial by Alvin H. Follingstad, from the Jan. 2, 1978, issue of *JAMA*, pages 29-30, "Estriol, the forgotten estrogen?" is being circulated to promote the use of estriol, or the phytoestrogens. It argues that women who secrete larger amounts of estriol are resistant to cancer.

By some tests, estriol is a "weak estrogen," by others it is a powerful estrogen.

When estriol was placed in the uterus of a rabbit, only 1.25 mcg. was sufficient to prevent implantation and destroy the blastocyst. (Dmowski, et al., 1977.) Since the effect was local, the body weight of

the animal doesn't make much difference, when thinking about the probable effect of a similar local contentration of the hormone on human tissues. The anti-progestational activity of estriol and estradiol are approximately the same. (Tamotsu and Pincus, 1958.)

When 5 mg. of estriol was given to women intravaginally, this very large dose suppressed LH within 2 hours, and suppressed FSH in 5 hours. Given orally, 8 mg. had similar effects on LH and FSH after 30 days, and also had an estrogenic effect on the vaginal epithelium.. These quick systemic effects of a "weak estrogen" are essentially those of a strong estrogen, except for the size of the dose. (Schiff, et al., 1978.)

When administered subcutaneously, estriol induced abortions and stillbirths (Velardo, et al.)

Another indication of the strength of an estrogen is its ability to cause the uterus to enlarge. Estriol is slightly weaker, in terms of milligrams required to cause a certain rate of uterine enlargement, than estradiol. (Clark, et al., 1979.) But isn't the important question whether or not the weak estrogen imitates all of the effects of estradiol, including carcinogenesis and blood clotting, in addition to any special harmful effects it might have?

When added to long-term culture of human breast cancer cells, estriol stimulated their growth, and overcame the antiestrogenic effects of tamoxifen, even at concentrations hundreds of times lower than that of tamoxifen. "The data do not support an antiestrogenic role for estriol in human breast cancer." (Lippman, et al., 1977.)

Studies of the urinary output of estriol/estradiol in women with or without breast cancer do not reliably show the claimed association between low estriol/estradiol and cancer, and the stimulating effect of estriol on the growth of cancer cells suggests that any alteration of the estrogen ratio is likely to be a *consequence* of the disease, rather than a cause. The conversion of estradiol to other estrogens occurs mainly in the liver, in the non-pregnant woman, as does the further metabolism of the estrogens into glucuronides and sulfates. The hormonal conditions leading to and associated with breast cancer all affect the liver and its metabolic systems. The hydroxylating enzymes are also affected by toxins. Hypothyroidism (low T3), low progesterone, pregnenolone, DHEA, etiocholanolone, and high prolactin, growth hormone, and cortisol are associated with the chronic high estrogen and breast cancer physiologies, and modify the liver's regulatory ability.

The decreased output of hormones when the fetal-placental system is dying is a natural consequence, since the placenta produces

hormones, and during pregnancy converts estradiol to estriol. Since estradiol in excess kills the fetus, its conversion by the placenta to estriol is in accord with the evidence showing that estriol is the more quickly excreted form. (G. S. Rao, 1973.) The conversion of 16-hydroxy androstenedione and 16-hydroxy-DHEA into estriol by the placenta (Vega Ramos, 1973) would also cause fetal exhaustion or death to result in lower estriol production. But a recent observation that a surge of estriol production precedes the onset of labor, and that its premature occurrence can identify women at risk of premature delivery (McGregor, et al., 1995) suggests that the estriol surge might reflect the mother's increased production of adrenal androgens during stress. (This would be analogous to the situation in the polycystic ovary syndrome, in which excessive estradiol drives the adrenals to produce androgens.)

Estetrol, which has one more hydroxyl group than estriol, is a "more sensitive and reliable indicator of fetal morbidity than estriol during toxemic pregnancies," because it starts to decrease earlier, or decreases more, than estriol. (Kundu, et al., 1978.) This seems to make it even clearer that the decline of estriol is a consequence, not a cause, of fetal sickness or death.

A 1994 publication (B. Zumoff, "Hormonal profiles in women with breast cancer," *Obstet. Gynecol. Clin. North. Am. (U.S.) 21(4)*, 751-772) reported that there are four hormonal features in women with breast cancer: diminished androgen production, luteal inadequacy, increased 16-hydroxylation of estradiol, and increased prolactin. The 16-hydroxylation converts estradiol into estriol.

A new technique for radiographically locating a hormone-dependent breast cancer is based on the fact that estriol-sulfate is a major metabolite of estradiol. The technique showed the tumor to have about a six times higher concentration of estriol-sulfate than liver or muscle. (N. Shimura, et al., "Specific imaging of hormone-dependent mammary carcinoma in nude mice with [^{131}I]-anti-estriol 3-sulfate antibody," *Nucl. Med. Biol. (England) 22(5)*, 547-553, 1995.)

Another association of elevated conversion of estradiol to estriol with disease was found to occur in men who had a myocardial infarction, compared to controls who hadn't. (W. S. Bauld, et al., 1957.)

The estrogens in clover have been known for several decades to have a contraceptive action in sheep, and other phytoestrogens are known to cause deformities in the genitals, feminization of men, and anatomical changes in the brain as well as functional masculinization of the female brain. (Register, et al., 1995; Levy, et al, 1995; Clarkson, et al., 1995;

Gavaler, et al., 1995.) The effects of the phytoestrogens are very complex, because they modify the sensitivity of cells to natural estrogens, and also modify the metabolism of estrogens, with the result that the effects on a given tissue can be either pro-estrogenic and anti-estrogenic. For example, the flavonoids, naringenin, quercetin and kaempherol (kaempherol is an antioxidant, a phytoestrogen, and a mutagen) modify the metabolism of estradiol, causing increased bioavailability of both estrone and estradiol. (W. Schubert, et al., "Inhibition of 17-beta-estradiol metabolism by grapefruit juice in ovariectomized women," *Maturitas (Ireland) 30(2-3)*, 155-163, 1994.)

Since phenolic compounds often function as "antioxidants," as well as estrogens, we are seeing an epidemic of marketing claims for plant substances that are "better than vitamin E" and "better than Premarin," but something that these super-antioxidants have in common with all estrogens is that they are easily oxidized, forming cycles of oxidation-reduction that consume oxygen, waste energy, and produce immense quantities of free radicals, causing genetic damage as well as other changes. That the damage might lead to cancer or seizures is bad enough, but the awful thing is that some of the changes are passed on in heredity, as cancer, or anatomical or neurological abnormalities.. L.C. Strong pioneered in the study of the hereditary toxicity of estrogen, generations ago, and transgenerational effects have been seen with DES and other estrogens.

Why do plants make phytoestrogens? There is some information indicating that these compounds evolved to regulate the plants' interactions with other organisms--to attract bacteria, or to repel insects, for example, rather than just as pigment-forming materials. (Baker, 1995.) The fact that some of them bind to our "estrogen receptors" is probably misleading, because of their many other effects, including inhibiting enzyme functions involved in the regulation of steroids and prostaglandins. Their biochemistry in animals is much more complicated than that of natural estrogens, which is itself so complicated that we can only guess what the consequences might be when we change the concentration and the ratio of substances in that complex system. (See quotation from Velardo, et al., page 6)

These "natural" effects in sheep were forerunners of the observed estrogenic effects in wild animals, caused by pollutants. Twenty-five years ago I reviewed many of the issues of estrogen's toxicity, and the ubiquity of estrogenic substances, and since then have regularly spoken about it, but I haven't concentrated much attention on the phytoestrogens,

because we can usually just choose foods that are relatively free of them. They are so often associated with other food toxins--antithyroid factors, inhibitors of digestive enzymes, immunosuppressants, etc.--that the avoidance of certain foods is desirable. Recently an advocate of soybeans said "if they inhibit the thyroid, why isn't there an epidemic of hypothyroidism in Asia?" I happened to hear this right after seeing newspaper articles about China's problem with 100,000,000 cretins; yes, Asia has endemic hypothyroidism, and beans are widely associated with hypothyroidism.

When I first heard about clover-induced miscarriages in sheep, I began reading about the subject, because it was relevant to the work I was doing at that time on reproductive aging. Sheep which are adapted to living at high altitude, where all animals have reduced fertility, have an adaptive type of hemoglobin, with a greater affinity for oxygen. Fetal hemoglobin, in animals at sea-level, has a great affinity for oxygen, making it possible for the fetus to get enough oxygen, despite its insulation from the mother's direct blood supply. The high-altitude-tolerant sheep have hemoglobin which is able to deliver sufficient oxygen to the uterus to meet the needs of the embryo/fetus, even during relative oxygen-deprivation. These sheep are able to sustain pregnancy while grazing on clover. It seemed evident that estrogen and high altitude had something in common, namely, oxygen deprivation, and it also seemed evident that these sheep provided the explanation for estrogen's abortifacient effects.

Estrogen's effects, ranging from shock to cancer, all seem to relate to an interference with the use of oxygen. Different estrogens have different affinities for various tissues, and a given substance is likely to have effects other than estrogenicity, and the presence of other substances will modify the way a tissue responds, but the stressful shift away from oxidative production of energy is the factor that all estrogens have in common. Otherwise, how could suffocation and x-irradiation have estrogenic effects?

Pharmaceutical misrepresentations regarding the estrogens rank, in terms of human consequences, with the radiation damage from fall-out from bomb tests and reactor-leaks, with industrial pollution, with degradation of the food supply--with genocide, in fact.

Advertising gets a bad name when it can't be distinguished from mass murder. At a certain point, we can't afford to waste our time making subtle distinctions between ignorance and malevolence. If we begin pointing out the lethal consequences of "stupid" or quasi-stupid

commercial/governmental policies, the offenders will have the burden of proving that their actions are the result of irresponsible ignorance, rather than criminal duplicity. From the tobacco senators to the chemical/pharmaceutical/food/energy industries and their agents in the governmental agencies, those who do great harm must be held responsible.

The idea of corporate welfare, in which public funds are given in massive subsidies to rich corporations, is now generally recognized. Next, we have to increase our consciousness of corporate responsibility, and that ordinary criminal law, especially RICO, can be directly applied to corporations. It remains to be seen whether a government can be made to stop giving public funds to corporations, and instead, to begin enforcing the law against them--and against those in the agencies who participated in their crimes.

In the U.S., the death penalty is sometimes reserved for "aggravated homicide." If those who kill hundreds of thousands for the sake of billions of dollars in profits are not committing aggravated homicide, then it must be that no law written in the English language can be objectively interpreted, and the legal system is an Alice in Wonderland convenience for the corporate state.

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given hormone combination may evoke differing levels of response in different target organs, and particularly, that increase of one component may increase response at one site while decreasing it at another. Many steroids...are present in the mammalian circulation during various phases of the sex cycle and are known to modify the effects of any given estrogen. This hormonal multiplicity apparently constitutes an estrogen-buffering system and supports the hypothesis that sexual responses depend '...upon a rather precise hormonal homeostasis.'"

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"Capture occurs when agencies informally promote the very interests they are officially responsible for regulating." In 1925, Coolidge's appointment of "anti-public" W. E. Humphrey to the FTC led some of its former supporters to call for the abolition of the FTC.

"If nearly a century of regulatory history tells us anything, it is that the rules-making agencies of government are almost invariably captured by the industries which they are established to control." Robert Heilbroner, In the Name of Profit, 1972, p. 239. "Federal economic regulation was generally designed by the regulated interest to meet its own end, and not those of the public or the commonweal." Gabriel Kolko, *The Triumph of Conservatism: A Reinterpretation of American History, 1900-1916,* 1963.

"It is a given in the modern doctrine of most tort laws that the existence of potential liability if anything encourages citizens to use greater thoughtfulness and care in their daily actions, and no obvious reasons suggest the same dynamic should not affect public officials." Adm. Law. & Pols., p. 404. "That Congress decided, after the passage of the Fourteenth Amendment, to enact legislation specifically requiring state officials to respond in federal court for their failures to observe the constitutional limitations on their powers is hardly a reason for excusing their federal counterparts for the identical constitutional transgressions." **"In situations of abuse, an action for damages against the responsible official can be an important means of vindicating constitutional guarantees...." Justice White, Butz v. Economou, p. 409, Adm. Law & Pols.**

26
SUNLIGHT: USING IT TO ENHANCE LIFE

GLOSSARY:

Mutations are changes in DNA molecules which can kill cells, or accelerate their aging, or contribute to the development of cancer.

Cellular respiration: the ability of cells to consume oxygen and produce useful biological energy.

Free radicals are parts of molecules that can be produced by radiation (including sunlight), which contribute to cells' aging, cancer, and mutations.

The **thymus gland** is an essential part of our immune system, and it shrinks when we don't get enough light.

Melatonin, or pineal hormone: the pineal gland in the brain responds to an absence of light (or to any stress which increases the adrenalin systems) by secreting a hormone called melatonin, which lightens the skin, makes the brain sluggish, turns off thyroid and progesterone production, and suppresses immunity and fertility.

Immunosuppression refers to any process that lowers the efficiency of our immune system, such as stress, radiation, or poisoning.

Q: You mention sunlight as beneficial to your health. How?

For example, it can cure depression, improve immunity, stimulate our metabolism while decreasing food craving, and increase our intelligence.

Although exposure to sun does contribute to aging of the skin, people who spend years working outdoors have a reduced incidence of cancer of internal organs. For many years, it has been known that the death rate increases during the winter months and also increases at night (winter *or* summer). Most deaths occur just before dawn when the body is in its least efficient state. It is just in the last few decades that we have been learning the reasons for this beneficial effect of light. It turns out that daylight stimulates our ability to use oxygen for energy production, and protects our tissues from some of the free-radical toxins that are produced by normal metabolism, by stress, or by radiation.

While ultraviolet light, and even blue light, tend to suppress our cells' ability to produce energy, those types of light penetrate only a short distance into living tissue, and so it is mainly the skin which is damaged by too much sunlight. Since blood does circulate in the layers of skin which receive ultraviolet rays, prolonged sun exposure can damage the immune system by injuring white blood cells, but usually the stimulating effect of the other types of light that penetrate more deeply offset this effect on the immune system.

Many health food stores are now selling melatonin, to induce sleep and "prevent cancer." They have taken some information out of context, and don't realize how dangerous melatonin is. It makes the brain sluggish, causes the sex organs to shrink, and damages immunity by shrinking the thymus gland. It suppresses thyroid and progesterone, and increases estrogen. It is the hormone of darkness and winter, and is produced in the pineal gland by *any stress* which increases adrenalin. Adequate sunlight suppresses the formation of melatonin.

This means that the immune system is most responsive in the summer, when days are long. Daylight stops the stress reaction, and protects our immune system.

Long hours of daylight increase progesterone production, and this contributes to a sense of well-being, and to the protection of all our tissues.

Q: Doesn't exposure to the sun age you?

This effect is variable, and depends on our hormones and diet.

The unsaturated oils have been identified as a major factor in skin aging. For example, two groups of rabbits were fed diets containing either corn oil or coconut oil, and their backs were shaved, so sunlight could fall directly onto their skin. The animals that ate corn oil developed prematurely wrinkled skin, while the animals that ate coconut oil didn't show any harm from the sun exposure. In a study at the University of California, photographs of two groups of people were selected, pairing people of the same age, one who had eaten an unsaturated fat rich diet, the other who had eaten a diet low in unsaturated fats. A panel of judges was asked to sort them by their apparent ages, and the subjects who consumed larger amounts of the unsaturated oils were consistently judged to be older than those who ate less, showing the same age-accelerating effects of the unsaturated oils that were demonstrated by the rabbit experiments.

While it is important to avoid overexposure to ultraviolet light, the skin damage that we identify with aging is largely a product of our diet.

Q: Don't you have to avoid sunlight because of skin cancer?

The type of skin cancer which is clearly caused by sunlight is a relatively harmless type of cancer, which appears only in sun-damaged skin. Melanoma, which is often called a skin cancer, because it sometimes begins in moles, does not have such a simple relationship to sunlight, and its incidence is significantly increased by the use of estrogen.

It is often said that the great increase in deaths from melanoma during the last 60 years has been caused by an increased popularity of sunbathing, but during the same time there has been a great increase in the incidence of cancer of the prostate, which is in a location that gets very little exposure to light. What these two cancers have in common is a sensitivity to estrogen, and it is during this same period of time that we have been exposed to increased amounts of estrogen-like chemicals in the environment as a result of industrial pollution: Dioxins, phenols, chlorinated hydrocarbons, DDT, smoke, etc. It is likely that these cancers (and others) are caused by the estrogenic pollutants.

The incidence of melanoma is consistently lower at greater elevations, where ultraviolet light is more intense, than at lower elevations. It is common for melanoma to develop on relatively shaded areas, including the middle of the back and the inside of the thigh, unlike the ordinary less malignant skin cancers, which develop most often on the forehead, nose, ear, cheek, and lip, where sun exposure is greatest. People who work outside have a low incidence of melanoma according to some studies, and this is sometimes said to be because they don't get sunburned, as pale people do when they spend time in the sun after being indoors for long periods. Sunburn does cause freckling, which is a clumping of pigment cells, but recent studies show that children who get sunburned are not at increased risk for melanoma. Sunburn causes complex changes in the tissue, including weakened immunity.

To avoid the aging and immunosuppressive effects of sunlight, it seems best for sunlight to come through a window glass which removes most of the ultraviolet light, and some of the blue light. Plastic film is available which contains copper that removes this harmful part of sunlight, and can be applied to ordinary window glass. Sitting in sunlight coming through a window of this sort, for short times during the day, is

very protective. Besides protecting against cancer, it helps to keep the mood and energy level high, by keeping melatonin low and stimulating metabolism.

Recently, the polyunsaturated oils have been identified as the main thing in cells that radiation interacts with, to cause cellular damage. Vitamin E, taken internally or even applied to the skin, has been found to reduce the damage produced by exposure to ultraviolet radiation, which is logical, since it interrupts the chain reactions of toxic free-radicals produced when unsaturated oils are oxidized by radiation or other injury. Aspirin has been found to have a similar effect in reducing the harmful effects which develop in the skin after sunlight over-exposure. Coconut oil has been used for generations in "suntan lotions," and whether it is absorbed through the skin or eaten as a food, it clearly has a protective antioxidant function. Carotene seems to work with vitamin E in the skin to reduce injury by ultraviolet radiation. Caffeine also has shown a protective action against radiation, but its mechanism of action isn't clearly understood.

Q: Why not use sun-blockers, so you can get light without getting burned?

If a sunscreen lotion is based on the use of an opaque reflective material, such as zinc oxide or titanium oxide, that substance remains mostly on the surface of the skin. This should make it fairly harmless, though it is possible that traces of titanium could be absorbed with oils into the skin, where it could be made toxic by interaction with ultraviolet rays.

However, other chemicals used in the sunscreen lotions, such as PABA derivatives, also react dangerously with light, and are easily absorbed in significant quantities into the deeper layers of the skin, where they can cause mutations.

For example, several recent studies have found that the sun-blockers, which decrease the ordinary skin damage caused by ultraviolet rays, actually increase the risk of developing melanoma, by causing mutations when the cells' chromosomes interact with the sunscreen and the light. (Something similar happens in the disease, porphyria. A pigment that accumulates causes the skin to become very sensitive to the sun. Estrogen is known to intensify the disease.)

Even natural colored compounds, which have sometimes been used in suntan lotions, should be avoided, since they might be able to transmit the energy of light to the chromosomes, causing mutations.

Radiation from the sun reacts with the unsaturated fats you have eaten to cause oxidative damage to skin cells. Vitamin E, vitamin A and carotene are antioxidants that prevent skin cell damage, when they are taken internally or applied to the surface of the skin.. None of these causes any harmful effects in the sun.

Aspirin reduces the iron content of the blood serum, and also inhibits the formation of the sometimes-toxic prostaglandins from fatty acids. Coconut oil is very resistant to radiation damage and, like vitamin E, tends to stop the chain reactions that occur in unsaturated fats. The old formula for suntan oil, cocount oil with iodine, might turn out to be a safe sunscreen, since the brown iodine absorbs light, as other "U.V. blockers" do, but iodine is also an effective chain breaker that inactivates free radicals, and it can't be absorbed into cells in its brown form. It doesn't have the potential for causing cancer that the popular sunscreens do.

Q: Is sunlight still beneficial if you use a safe sun blocker?

The popular chemical sun blockers are meant to stop the ultraviolet rays. If they can do that, without increasing the risk of melanoma, then they are very beneficial, because this will allow you to get a long exposure to direct sunlight, which penetrates deeply and has an antistress effect. But so far, there is no research that shows any of the chemical ultraviolet blockers is safe.

Q: Why do people seem to get sicker in the wintertime, often right after Christmas?

Nights are much longer in the winter, and even in the summer, death rates are higher during the night than in daytime. December 21 is the day with the fewest hours of sunlight, but the cumulative damage of prolonged darkness reaches its peak about a month later. Cold temperatures do have some harmful effects, but by keeping people indoors, or bundled up in thick clothing, cold weather also causes us to get very little exposure to sunlight. Winter sickness is mainly the result of a "light deficiency."

When young sailors spent 6 months in the continuous polar night of Antarctica, they developed the same signs of nocturnal stress that are common in old people during the night. Many old people habitually get up before dawn, because they find it impossible to stay asleep. Even healthy young people (and animals) experience some degree of nocturnal stress as soon as the light is turned off at night, and their body responds with an increased production of adrenalin and cortisol.

The energy-producing part of cells, the mitochondrion, shows signs of being increasingly damaged as the night progresses, but they are gradually restored to their normal condition during the daytime light hours. This means that our greatest ability to resist stress is in the late afternoon, and we are most susceptible to injury at dawn. In the winter, nights are long and days are short, so we experience a cumulative increase in our susceptibility to stress-injury during the winter months.

The light which penetrates deeply into our tissues (mainly orange and red light) is able to improve the efficiency of energy production, and to suppress the toxic free-radicals that are always being formed in cells.

Q: Can you get enough sunlight during the summer to hold you through the winter?

No, many of the beneficial effects of bright light disappear during just a few hours of darkness, though the restoration of our tissues that happens during the summer puts us into a better state for surviving the winter, for example by allowing massive regeneration of the thymus to occur. (This occurs in adults, not just in children. The idea that the thymus disappears after puberty is based on autopsies. If a person lives for even 3 hours after an accident or the onset of sickness, the thymus has had time to shrink.)

Frequent short exposures to bright light is almost as valuable as continuous sunlight, and it is less likely to cause skin aging.

Q. How much sunlight do we need a day for general health?

If artificial light is bright enough, it is as effective as sunlight at stopping the stress reaction, but people seldom use lights that are bright enough. Generally, people and animals are healthier when days are longer than 12 hours, that is, after March 21 and before September 20. When days are shorter than 12 hours, artificial lights should be used from sunset until bedtime, but the greatest brightness probably doesn't have to be continuous. Studies on isolated organs and tissues suggest that a few

seconds of penetrating bright light are enought to break the free radical chain reactions, slowing the production of toxic substances, which tend to increase in concentration during nocturnal stress. A few seconds' exposure to the direct light of ten 150 Watt incandescent bulbs, for just a few minutes every two or three hours, might provide more effective protection than continuous exposure to a single 100 Watt light.

SUMMARY

In fall and winter, use very bright incandescent lights daily from sunset until bedtime.

Expose as much skin as possible to the bright light; even a minute is better than nothing. Thin, light-colored clothing transmits a considerable amount of light.

Infrared bulbs, with clear glass, are especially beneficial. Special low temperature red lights are available.

It is better to get your sunlight through windows, because it has less ultraviolet light than direct sunlight.

Don't use sun-blocking lotions, other than the simply reflective type (zinc oxide or titanium oxide).

Decrease the use of unsaturated oils in the diet, and use coconut oil as food and also on the skin during exposure to direct sunlight.

Vitamin E and aspirin reduce the harmful effects of sunburn, even when used after exposure to the sun, they can be applied topically to the burned skin. Vitamin E often contains some soy oil, so I recommend small doses of about 100 mg. per day.

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27
UNSATURATED VEGETABLE OILS: TOXIC

GLOSSARY:

Immunodeficiency (weakness of the immune system) can take many forms. *AIDS*, for example, refers to an immunodeficiency which is "acquired," rather than "inborn." Radiation and vegetable oils can cause "acquired immunodeficiency." Unsaturated oils, especially polyunsaturates, weaken the immune system's function in ways that are similar to the damage caused by radiation, hormone imbalance, cancer, aging, or viral infections. The media discuss sexually transmitted and drug-induced immunodeficiency, but it isn't yet considered polite to discuss vegetable oil-induced immunodeficiency.

Unsaturated oils: When an oil is saturated, that means that the molecule has all the hydrogen atoms it can hold. Unsaturation means that some hydrogen atoms have been removed, and this opens the structure of the molecule in a way that makes it susceptible to attack by free radicals.

Free radicals are reactive molecular fragments that occur even in healthy cells, and can damage the cell. When unsaturated oils are exposed to free radicals they can create chain reactions of free radicals that spread the damage in the cell, and contribute to the cell's aging.

Rancidity of oils occurs when they are exposed to oxygen, in the body just as in the bottle. Harmful free radicals are formed, and oxygen is used up.

Essential fatty acids (EFA) are, according to the textbooks, linoleic acid and linolenic acid, and they are supposed to have the status of "vitamins," which must be taken in the diet to make life possible. However, we are able to synthesize our own unsaturated fats when we don't eat the "EFA," so they are not "essential." The term thus appears to be a misnomer. [M. E. Hanke, "Biochemistry," Encycl. Brit. Book of the Year, 1948.]

Q: You say vegetable oils are hazardous to your health. What vegetable oils are you talking about?

Mainly, I'm referring to soybean oil, corn oil, safflower oil, canola, sesame oil, sunflower seed oil, palm oil, and any others that are labeled as "unsaturated" or "polyunsaturated." Almond oil, which is used in many cosmetics, is very unsaturated.

Chemically, the material that makes these oils very toxic is the polyunsaturated fat itself. These unsaturated oils are found in very high concentrations in many seeds, and in the fats of animals that have eaten a diet containing them. The fresh oils, whether cold pressed or consumed as part of the living plant material, are intrinsically toxic, and it is not any special industrial treatment that makes them toxic. Since these oils occur in other parts of plants at lower concentration, and in the animals which eat the plants, it is impossible to eat a diet which lacks them, unless special foods are prepared in the laboratory.

These toxic oils are sometimes called the "essential fatty acids" or "vitamin F," but this concept of the oils as essential nutrients was clearly disproved over 50 years ago.

Linoleic and linolenic acids, the "essential fatty acids," and other polyunsaturated fatty acids, which are now fed to pigs to fatten them, in the form of corn and soy beans, cause the animals' fat to be chemically equivalent to vegetable oil. In the late 1940s, chemical toxins were used to suppress the thyroid function of pigs, to make them get fatter while consuming less food. When that was found to be carcinogenic, it was then found that corn and soy beans had the same antithyroid effect, causing the animals to be fattened at low cost. The animals' fat becomes chemically similar to the fats in their food, causing it to be equally toxic, and equally fattening.

These oils are derived from seeds, but their abundance in some meat has led to a lot of confusion about "animal fats." Many researchers still refer to lard as a "saturated fat," but this is simply incorrect when pigs are fed soybeans and corn.

Q: How are these oils hazardous to your health?

Ultimately, all systems of the body are harmed by an excess of these oils. There are two reasons for this. One is that the plants produce the oils for protection, not only to store energy for the germination of the seed. To defend the seeds from the animals that would eat them, the oils block the digestive enzymes in the animals' stomachs. Digestion is one of our most basic functions, and evolution has built many other systems by

using variations of that system; as a result, all of these systems are damaged by the substances which damage the digestive system.

The other reason is that the seeds are designed to germinate in early spring, so their energy stores must be accessible when the temperatures are cool, and they normally don't have to remain viable through the hot summer months. Unsaturated oils are liquid when they are cold, and this is necessary for any organism that lives at low temperatures. For example, fish in cold water would be stiff if they contained saturated fats. These oils easily get rancid (spontaneously oxidizing) when they are warm and exposed to oxygen. Seeds contain a small amount of vitamin E to delay rancidity. When the oils are stored in our tissues, they are much warmer, and more directly exposed to oxygen, than they would be in the seeds, and so their tendency to oxidize is very great. These oxidative processes can damage enzymes and other parts of cells, and especially their ability to produce energy.

The enzymes which break down proteins are inhibited by unsaturated fats, and these enzymes are needed not only for digestion, but also for production of thyroid hormones, clot removal, immunity, and the general adaptability of cells. The risks of abnormal blood clotting, inflammation, immune deficiency, shock, aging, obesity, and cancer are increased. Thyroid and progesterone are decreased. Since the unsaturated oils block protein digestion in the stomach, we can be malnourished even while "eating well."

Plants produce many protective substances to repel or injure insects and other animals that eat them. They produce their own pesticides. The oils in seeds have this function. On top of this natural toxicity, the plants are sprayed with industrial pesticides, which can concentrate in the seed oils.

It isn't the quantity of these polyunsaturated oils which governs the harm they do, but the relationship between them and the saturated fats. Obesity, free radical production, the formation of age pigment, blood clotting, inflammation, immunity, and energy production are all responsive to the ratio of unsaturated fats to saturated fats, and the higher this ratio is, the greater the probability of harm there is.

There are interesting interactions between these oils and estrogen. For example, puberty occurs at an earlier age if estrogen is high, or if these oils are more abundant in the diet. This is probably a factor in the development of cancer.

All systems of the body are harmed by an excess of these oils. There are three main kinds of damage: one, hormonal imbalances, two, damage to the immune system, and three, oxidative damage.

Q: How do they cause hormonal imbalances?

There are many changes in hormones caused by unsaturated fats. Their best understood effect is their interference with the function of the thyroid gland. Unsaturated oils block thyroid hormone secretion, its movement in the circulatory system, and the response of tissues to the hormone. When the thyroid hormone is deficient, the body is generally exposed to increased levels of estrogen. The thyroid hormone is essential for making the "protective hormones" progesterone and pregnenolone, so these hormones are lowered when anything interferes with the function of the thyroid. The thyroid hormone is required for using and eliminating cholesterol, so cholesterol is likely to be raised by anything which blocks the thyroid function. [B. Barnes and L. Galton, Hypothyroidism, 1976, and 1994 references.]

Q: How do they damage the immune system?

Vegetable oil is recognized as a drug for knocking out the immune system. Vegetable oil emulsions were used to nourish cancer patients, but it was discovered that the unsaturated oils were suppressing their immune systems. The same products, in which vegetable oil is emulsified with water for intravenous injection, are now marketed specifically for the purpose of suppressing immunity in patients who have had organ transplants. Using the oils in foods has the same harmful effect on the immune system. [E. A. Mascioli, et al.,Lipids 22(6) 421, 1987.] Unsaturated fats directly kill white blood cells. [C. J. Meade and J. Martin, Adv. Lipid Res., 127, 1978.]

Q: How do they cause oxidative damage?

Unsaturated oils get rancid when exposed to air; that is called oxidation, and it is the same process that occurs when oil paint "dries." Free radicals are produced in the process.

This process is accelerated at higher temperatures. The free radicals produced in this process react with parts of cells, such as

molecules of DNA and protein and may become attached to those molecules, causing abnormalities of structure and function.

Q: What if I eat only organically grown vegetable oils?

Even without the addition of agricultural chemicals, an excess of unsaturated vegetable oils damages the human body. Cancer can't occur, unless there are unsaturated oils in the diet. [C. Ip, et al., Cancer Res. 45, 1985.] Alcoholic cirrhosis of the liver cannot occur unless there are unsaturated oils in the diet. [Nanji and French, Life Sciences. 44, 1989.] Heart disease can be produced by unsaturated oils, and prevented by adding saturated oils to the diet. [J. K. G. Kramer, et al., Lipids 17, 372, 1983.]

Q. What oils are safe?

Coconut and olive oil are the only vegetable oils that are really safe, but butter and lamb fat, which are highly saturated, are generally very safe (except when the animals have been poisoned). Coconut oil is unique in its ability to prevent weight-gain or cure obesity, by stimulating metabolism. It is quickly metabolized, and functions in some ways as an antioxidant. Olive oil, though it is somewhat fattening, is less fattening than corn or soy oil, and contains an antioxidant which makes it protective against heart disease and cancer.

Israel had the world's highest incidence of breast cancer when they allowed the insecticide lindane to be used in dairies, and the cancer rate decreased immediately after the government prohibited its use. The United States has fairly good laws to control the use of cancer-causing agents in the food supply, but they are not vigorously enforced. Certain cancers are several times more common among corn farmers than among other farmers, presumably because corn "requires" the use of more pesticides. This probably makes corn oil's toxicity greater than it would be otherwise, but even the pure, organically grown material is toxic, because of its intrinsic unsaturation.

In the United States, lard is toxic because the pigs are fed large quantities of corn and soy beans. Besides the intrinsic toxicity of the seed oils, they are contaminated with agricultural chemicals. Corn farmers have a very high incidence of cancer, presumably because of the pesticides they use on their crop.

Although I don't recommend "palm oil" as a food, because I think it is less stable than coconut oil, some studies show that it contains valuable nutrients. For example, it contains antioxidants similar to vitamin E, which lower both LDL cholesterol and a platelet clotting factor. [B. A. Bradlow, University of Illinois, Chicago; Science News 139, 268, 1991.] Coconut oil and other tropical oils also contain some hormones that are related to pregnenolone or progesterone.

Q: Isn't coconut oil fattening?

Coconut oil is the least fattening of all the oils. Pig farmers tried to use it to fatten their animals, but when it was added to the animal feed, coconut oil made the pigs lean [See Encycl. Brit. Book of the Year, 1946].

Q: What about olive oil? Isn't it more fattening than other vegetable oils?

In this case, as with coconut oil, "fattening" has more to do with your ability to burn calories than with the caloric value of the oil. Olive oil has a few more calories per quart than corn or soy oil, but since it doesn't damage our ability to burn calories as much as the unsaturated oils do, it is less fattening. Extra virgin olive oil is the best grade, and contains an antioxidant that protects against cancer and heart disease. [1994, Curr. Conts.]

Q: Does that mean that using olive oil helps to prevent cancer?

Some studies in Europe suggest that, but studies in animals show that when the total calorie intake is excessive, even a small amount of linoleic acid is enough to increase the incidence of cancer, and olive oil contains some linoleic acid. The people who use more olive oil might eat less bread and pasta, and as a result might be less obese, and so less likely to get cancer. Eating any fat with a starch makes the starch less harmful, and it's clearly better to use olive oil than the more highly polyunsaturated seed oils.

Q: Is "light" olive oil okay?

No. Now and then someone learns how to make a profit from waste material. "Knotty pine" boards were changed from a discarded material to a valued decorative material by a little marketing skill. Light olive oil is a low grade material which sometimes has a rancid smell and probably shouldn't be used as food.

Q: Is margarine okay?

There are several problems with margarine. The manufacturing process introduces some toxins, including a unique type of fat which has been associated with heart disease. [Sci. News, 1974; 1991.] There are likely to be dyes and preservatives added to margarine. And newer products contain new chemicals that haven't been in use long enough to know whether they are safe.

However, the basic hardening process, hydrogenation of the oils, has been found to make the oils less likely to cause cancer. If I had to choose between eating ordinary corn oil or corn oil that was 100% saturated, to make a hard margarine, I would choose the hard margarine, because it resists oxidation, isn't suppressive to the thyroid gland, and doesn't cause cancer.

Q: What about butter?

Butter contains natural vitamin A and D and some beneficial natural hormones. It is less fattening than the unsaturated oils. There is much less cholesterol in an ounce of butter than in a lean chicken breast [about 1/5 as much cholesterol in fat as in lean meat on a calorie basis, according to R. Reiser of Texas A & M Univ., 1979].

Q: Are fish oils good for you?

Some of the unsaturated fats in fish are definitely less toxic than those in corn oil or soy oil, but that doesn't mean they are safe. Fifty years ago, it was found that a large amount of cod liver oil in dogs' diet increased their death rate from cancer by 20 times, from the usual 5% to 100%. A diet rich in fish oil causes intense production of toxic lipid peroxides, and has been observed to reduce a man's sperm count to zero. [H. Sinclair, Prog. Lipid Res. 25, 667, 1989.]

Q: What about lard?

In this country, lard is toxic beause the pigs are fed large quantities of corn and soy beans. Besides the natural toxicity of the seed oils, the oils are contaminated with agricultural chemicals. Corn farmers have a very high incidence of cancer, presumably because corn "requires" the use of more pesticides. This probably makes corn oil's toxicity greater than it would be otherwise. but even the pure, organically grown material is toxic, because of its unsaturation.

Women with breast cancer have very high levels of agricultural pesticides in their breasts [See Science News, 1992, 1994].

Israel had the world's highest incidence of breast cancer when they allowed the insecticide lindane to be used in dairies, and the cancer rate decreased immediately after the government prohibited its use. The United States has fairly good laws to control the use of cancer-causing agents in the food supply, but they are not vigorously enforced. [World Incid. of Cancer, 1992.]

Q: I have no control over oils when eating out. What can I do to offset the harmful effects of polyunsaturated oils?

A small amount of these oils won't kill you. It is the proportion of them in your diet that matters. A little extra vitamin E (such as 100 units per day) will take care of an occasional American restaurant meal. Based on animal studies, it would take a teaspoonful per day of corn or soy oil added to a fat-free diet to significantly increase our risk of cancer. Unfortunately, it is impossible to devise a fat-free diet outside of a laboratory. Vegetables, grains, nuts, fish and meats all naturally contain large amounts of these oils, and the extra oil used in cooking becomes a more serious problem.

Q Why are the unsaturated oils so popular if they are dangerous?

It's a whole system of promotion, advertising, and profitability.

50 years ago, paints and varnishes were made of soy oil, safflower oil, and linseed (flax seed) oil. Then chemists learned how to make paint from petroleum, which was much cheaper. As a result, the huge seed oil industry found its crop increasingly hard to sell. Around the same time, farmers were experimenting with poisons to make their pigs get fatter

with less food, and they discovered that corn and soy beans served the purpose, in a legal way. The crops that had been grown for the paint industry came to be used for animal food. Then these foods that made animals get fat cheaply came to be promoted as foods for humans, but they had to direct attention away from the fact that they are very fattening. The "cholesterol" focus was just one of the marketing tools used by the oil industry. Unfortunately it is the one that has lasted the longest, even after the unsaturated oils were proven to cause heart disease as well as cancer. [Study at L.A. Veterans Hospital, 1971.]

I use some of these oils (walnut oil is very nice, but safflower oil is cheaper) for oil painting, but I am careful to wash my hands thoroughly after I touch them, because they can be absorbed through the skin.

SUMMARY

Unsaturated fats cause aging, clotting, inflammation, cancer, and weight gain.

Avoid foods which contain the polyunsaturated oils, such as corn, soy, safflower, flax, cottonseed, canola, peanut, and sesame oil.

Mayonnaise, pastries, even candies may contain these oils; check the labels for ingredients.

Pork is now fed corn and soy beans, so lard is usually as toxic as those oils; use only lean pork.

Fish oils are usually highly unsaturated; "dry" types of fish, and shellfish, used once or twice a week, are good. Avoid cod liver oil.

Use vitamin E.

Use coconut oil, butter, and olive oil.

Unsaturated fats intensify estrogen's harmful effects.

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28
DANGERS OF IRON--EXACERBATED BY ESTROGEN

The questions in this chapter came from a two day conference in Indianapolis, in 1994.

GLOSSARY:

Free radicals are fragments of molecules that are very destructive to all cells and system of the body.

Respiration refers to the absorption of oxygen by cells, which releases energy. The structure inside the cell in which energy is produced by respiration is called the mitochondrion.

Oxidation refers to the combination of a substance with oxygen. This can be beneficial, as in normal respiration that produces energy, or harmful, as in rancidity, irradiation, or stress reactions.

Antioxidants: Vitamin E and vitamin C are known as antioxidants, because they stop the harmful free-radical chain reactions which often involve oxygen, but they do not inhibit normal oxidation processes in cells. **"Chain breaker"** would be a more suitable term. It is often the *deficiency* of oxygen which unleashes the dangerous free-radical processes. Many substances can function as antioxidants/chain breakers: thyroxine, uric acid, biliverdin, selenium, iodine, vitamin A, sodium, magnesium, and lithium, and a variety of enzymes. Saturated fats work with antioxidants to block the spread of free-radical chain reactions.

Age pigment is the brown material that forms spots on aging skin, and that accumulates in the lens of the eye forming cataracts, and in blood vessels causing hardening of the arteries, and in the heart and brain and other organs, causing their functions to deteriorate with age. It is made up of oxidized unsaturated oils with iron.

Anemic means lacking blood, in the sense of not having enough red blood cells or hemoglobin. It is possible to have too much iron in the blood while being anemic. Anemia in itself doesn't imply that there is a nutritional need for iron.

Q: You believe iron is a deadly substance. Why?

Iron is a potentially toxic heavy metal. In excess, it can cause cancer, heart disease, and other illnesses.

Q: Could you tell us about some of these studies?

In the 1960s the World Health Organization found that when iron supplements were given to anemic people in Africa, there was a great increase in the death rate from infectious diseases, especially malaria. Around the same time, research began to show that the regulation of iron is a central function of the immune system, and that this seems to have evolved because iron is a basic requirement for the survival and growth of cells of all types, including bacteria, parasites, and cancer. The pioneer researcher in the role of iron in immunity believed that an excess of dietary iron contributed to the development of leukemia and lymphatic cancers.

For about 50 years, it has been known that blood transfusions damage immunity, and excess iron has been suspected to be one of the causes for this. People who regularly donate blood, on the other hand, have often been found to be healthier than non-donors, and healthier than they were before they began donating.

Just like lead, mercury, cadmium, nickel, manganese and other heavy metals, stored iron produces destructive free radicals. The harmful effects of iron-produced free radicals are practically indistinguishable from those caused by exposure to X-rays and gamma rays; both accelerate the accumulation of age-pigment and other signs of aging. Excess iron is a crucial element in the transformation of stress into tissue damage by free radicals.

In one of Hans Selye's pioneering studies, he found that he could experimentally produce a form of scleroderma (hardening of the skin) in animals by administering large doses of iron, followed by a minor stress. He could prevent the development of the condition by giving the animals large doses of vitamin E, suggesting that the condition was produced by iron's oxidative actions.

Many recent studies show that iron is involved in degenerative brain diseases, such as Parkinson's, ALS (Lou Gehrig's disease), Huntington's chorea, and Alzheimer's disease. Iron is now believed to

have a role in skin aging, atherosclerosis, and cataracts of the lenses of the eyes, largely through its formation of the "age pigment."

Q: How does excess iron accelerate our aging process?

During aging, our tissues tend to store an excess of iron. There is a remarkably close association between the amount of iron stored in our tissues and the risk of death from cancer, heart disease, or from all causes. This relationship between iron and death rate exists even during childhood, but the curve is downward until the age of 12, and then it rises steadily until death. The shape of this curve, representing the iron burden, is amazingly similar to the curves representing the rate of death in general, and the rate of death from cancer. There is no other relationship in biology that I know of that has this peculiar shape, with its minimum at the age of 12, and its maximum in old age at the time of death.

One of the major lines of aging research, going back to the early part of this century, was based on the accumulation of a brown material in the tissues known as "age-pigment." The technical name for this material, "lipofuscin," means "fatty brown stuff." In the 1960s, the "free radical theory" of aging was introduced by Denham Harman, and this theory has converged with the age-pigment theory, since we now know that the age-pigment is an oxidized mass of unsaturated fat and iron, formed by uncontrolled free radicals. Until a few years ago, these ideas were accepted by only a few researchers, but now practically every doctor in the country accepts that free radicals are important in the aging process.

A nutrition researcher in San Diego suspected that the life-extending effects of calorie restriction might be the result of a decreased intake of toxins. **He removed the toxic heavy metals from foods, and found that the animals which ate a normal amount of food lived as long as the semi-starved animals. Recently, the iron content of food has been identified as the major life-shortening factor, rather than the calories.** [Choi and Yu, *Age* vol. 17, page 93, 1994.]

Q: Exactly how much iron do we need to eat?

Children's nutritional requirements are high, because they are growing, but there are indications that in the U.S. even children eat too much iron. Some researchers are concerned that the iron added to cereals is contributing to the incidence of leukemia and cancers of the lymphatic

tissues in children. [Goodfield, 1984.] During the time of rapid growth, children are less likely than adults to store too much iron. At birth, they have a large amount of stored iron, and this decreases as they "grow into it." It is after puberty, when growth slows and the sex hormones are high, that the storage of iron increases. [*Blood*, Sept., 1976.]

In a study of the "malnourished" children of migrant fruit pickers in California, these children who were "seriously anemic" were actually more resistant to infectious diseases than were the "well nourished" middle class children in the same region.

If the normal amount of dietary iron causes an increased susceptibility to infections even in children, and if a subnormal amount of iron slows the aging process, I think we are going to have to reconsider our ideas of nutritional adequacy, to look at the long range effects of diet, as well as the immediate effects. My current studies have to do with analyzing our ability to handle stress safely, in relation to our diet. I believe our nutritional recommendations for iron have to be revised sharply downward.

Q. Don't women need extra iron?

That's a misunderstanding. Doctors generally don't realize that only a few milligrams of iron are lost each day in menstruation. The real issue is that you can hardly avoid getting iron, even when you try.

Women absorb iron much more efficiently than men do. From a similar meal, women will normally absorb three times as much iron as men do. When pregnant, their higher estrogen levels cause them to absorb about nine times as much as men. Every time a woman menstruates, she loses a little iron, so that by the age of 50 she is likely to have less iron stored in her tissues than a man does at the same age, but by the age of 65 women generally have as much excess iron in their tissues as men do. (During those 15 years, women seem to store iron at a faster rate than men do, probably because they have more estrogen.) At this age their risk of dying from a heart attack is the same as that of men.

Some women who menstruate can donate blood regularly without showing any tendency to become anemic.

Since the custom of giving large iron supplements to pregnant women has been established, there has been an increase in jaundice of the newborn. It has been observed that women who didn't take iron supplements during pregnancy have healthy babies that don't develop jaundice. I have suggested that this could be because they haven't been

poisoned by iron. Those supplements could also be a factor in the increased incidence of childhood cancer.

Q: Don't you need iron supplements if you are anemic?

In general, no.

Many doctors think of anemia as necessarily indicating an iron deficiency, but that isn't correct. 100 years ago, it was customary to prescribe arsenic for anemia, and it worked to stimulate the formation of more red blood cells. The fact that arsenic, or iron, or other toxic material stimulates the formation of red blood cells doesn't indicate a "deficiency" of the toxin, but simply indicates that the body responds to a variety of harmful factors by speeding its production of blood cells. Even radiation can have this kind of stimulating effect, because growth is a natural reaction to injury. Between 1920 and 1950, it was common to think of "nutritional growth factors" as being the same as vitamins, but since then it has become common to use known toxins to stimulate the growth of farm animals, and as a result, it has been more difficult to define the essential nutrients. The optimal nutritional intake is now more often considered in terms of resistance to disease, longevity or rate of aging, and even mental ability.

An excess of iron, by destroying vitamin E and oxidizing the unsaturated fats in red blood cells, can contribute to hemolytic anemia, in which red cells are so fragile that they break down too fast. In aging, red cells break down faster, increasing the tendency to become anemic, but additional iron tends to be more dangerous for older people.

Anemia in women is caused most often by a thyroid deficiency (as discussed in the chapter on thyroid), or by various nutritional deficiencies. Estrogen (even in animals that don't menstruate) causes dilution of the blood, so that it is normal for females to have lower hemoglobin than males.

Q. What should I do if my doctor tells me I'm anemic? Is there any situation in which a person needs to take iron supplements?

Iron deficiency anemia does exist, in laboratory situations and in some cases of chronic bleeding, but I believe it should be the last-suspected cause of anemia, instead of the first. It should be considered as a possible cause of anemia only when very specific blood tests show an abnormally low degree of iron saturation of certain

proteins. Usually, physicians consider the amount of hemoglobin or of red cells in the blood as the primary indicator of a need for iron, but that just isn't biologically reasonable.

If a large amount of blood is lost in surgery, a temporary anemia might be produced, but even then it would be best to know whether the iron stores are really depleted before deciding whether an iron supplement would be reasonable. Liver (or even a water extract of wheat germ) can supply as much iron as would be given as a pill, and is safer.

Q. What foods contain iron?

Flour, pasta, etc., almost always contain iron which has been artificially added as ferrous sulfate, because of a federal law. Meats, grains, eggs, and vegetables naturally contain large amounts of iron. A few years ago, someone demonstrated that they could pick up a certain breakfast cereal with a magnet, because of the added iron. Black olives contain iron, which is used as a coloring material. You should look for "ferrous" or "ferric" or "iron" on the label, and avoid foods with any added iron. Many labels list "reduced iron," meaning that iron is added in the ferrous form, which is very reactive and easily absorbed.

Q.: Why does federal law require the addition of iron to those foods?

Industrially processed grains have most of the nutrients, such as vitamin E, the B vitamins, manganese, magnesium, etc., removed to improve the products' shelf life and efficiency of processing, and the government required that certain nutrients be added to them as a measure to protect the public's health, but the supplementation did not reflect the best science even when it was first made law, since food industry lobbyists managed to impose compromises that led to the use of the cheapest chemicals, rather than those that offered the greatest health benefits. For example, studies of processed animal food had demonstrated that the addition of iron (as the highly reactive form, ferrous sulfate, which happens to be cheap and easy to handle) created disease in animals, by destroying vitamins in the food. You should read the label of ingredients and avoid products that contain added iron, when possible.

Q: Can cooking in an iron frying pan put iron into food?

Yes, especially if the food is acidic, as many sauces are. The added iron will destroy vitamins in the food, besides being potentially toxic in itself.

Q: What about aluminum?

Aluminum and iron react similarly in cells and are suspected causes of Alzheimer's disease.

The aluminum industry started propagandizing more than 50 years ago about the "safety" of aluminum utensils, claiming that practically none of the toxic metal gets into the food. Recent research showed that coffee percolated in an aluminum pot contained a large amount of dissolved aluminum, because of coffee's acidity.

Q: What kinds of cooking pots or utensils are safe?

Glass utensils are safe, and certain kinds of stainless steel are safe, because their iron is relatively insoluble. Teflon-coated pans are safe unless they are chipped.

Q: How do I know which stainless steels are safe?

There are two main types of stainless steel, magnetic and nonmagnetic. The nonmagnetic form has a very high nickel content, and nickel is allergenic and carcinogenic. It is much more toxic than iron or aluminum. You can use a little "refrigerator magnet" to test your pans. The magnet will stick firmly to the safer type of pan.

Q: Why is there iron in most multi-vitamin and mineral products?

Although several researchers have demonstrated that iron destroys vitamins, there is enough wishful thinking in industry, government, and the consuming public, that such mistakes can go on for generations before anyone can mobilize the resources to bring the truth to the public. Ten years ago, I thought it was a hopeful sign of increased awareness of iron's danger when the manufacturer of a new iron product mentioned in the Physician's Desk Reference that it hadn't yet been reported to cause cancer.

Q. I can't avoid all those foods, especially the bread and grains. What can I do to keep the iron I ingest from harming me?

Iron destroys vitamin E, so vitamin E should be taken as a supplement. It shouldn't be taken at the same time as the iron-contaminated food, because iron reacts with it in the stomach. About 100 mg. per day is adequate, though our requirement increases with age, as our tissue iron stores increase. Coffee, when taken with food, strongly inhibits the absorption of iron, so I always try to drink coffee with meat. Decreasing your consumption of unsaturated fats makes the iron less harmful.

Vitamin C stimulates the absorption of iron, so it might be a good idea to avoid drinking orange juice at the same meal with iron-rich foods. A deficiency of copper causes our tissues to retain an excess of iron, so foods such as shrimp and oysters which contain abundant copper should be used regularly.

Q: How does copper help us?

Copper is the crucial element for producing the color in hair and skin, for maintaining the elasticity of skin and blood vessels, for protecting against certain types of free radical, and especially for allowing us to use oxygen properly for the production of biological energy. It is also necessary for the normal functioning of certain nerve cells (substantia nigra) whose degeneration is involved in Parkinson's disease. The shape and texture of hair, as well as its color, can change in a copper deficiency.

Too much iron can block our absorption of copper, and too little copper makes us store too much iron. With aging, our tissues lose copper as they store excess iron. Because of those changes, we need more vitamin E as we age.

SUMMARY:

Iron is a potentially toxic heavy metal; an excess can cause cancer, heart disease, and other illnesses.

Other heavy metals, including lead and aluminum, are toxic; pans and dishes should be chosen carefully.

Iron causes cell aging.

Drinking coffee with iron rich foods can reduce iron's toxic effects.

Use shrimp and oysters, etc., to prevent the copper deficiency which leads to excess storage of iron.

Avoid food supplements which contain iron.

Take about 100 units of vitamin E daily; your vitamin E requirement increases with your iron consumption.

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*A Finnish study, two years ago, indicated that high iron stores may increase heart attack risk: In People magazine, 1994: "Is iron a killer?" Dr. Jerome L. Sullivan, director of clinical labs of Veterans Affairs Medical Center at Charleston, S.C., in 1983 proposed that excess iron contributes to heart attacks. University of Kuopio in Finland: Large-scale study (nearly 2,000 men, for up to five years; next to smoking, excess stored iron is the most significant identifiable risk factor for heart attacks. It is a stronger risk factor for heart attack than high blood pressure and cholesterol.

*Dec. 7, page 6E, Register Guard (Eugene, OR): US studies showed a weak connection between iron and heart disease, and a weak connection with the iron in red meat. Epidemiologists at the Pacific Northwest Laboratory in Washington have reported that the greater the concentration of iron in a person's blood, the greater his or her risk of cancer. Richard Stevens and his co-workers found the connection from examining cancer rates in more

than 8,000 people who participated in the 1971 National Health and Nutrition Examination survey. A second Finnish study with similar findings accompanied Stevens's report in the International Journal of Cancer, and suggets that there may be cause for concern.

Register Guard (Eugene, OR), Jan. 16, 95; p 7A: Number of heart failures doubles, AP: 1982-92, heart disease death rate dropped 24.5%; number of cases of congestive heart failure doubled during roughly the same period. It killed 39,000 Americans in 1991, costs system $40 billion per year. Cancer is the biggest killer of women under 64, heart disease far surpasses cancer in women of ages 65-84.

29
COCONUT OIL

I have already discussed the many toxic effects of the unsaturated oils, and I have frequently mentioned that coconut oil doesn't have those toxic effects, though it does contain a small amount of the unsaturated oils. Many people have asked me to write something on coconut oil. I thought I might write a small book on it, but I realize that there are no suitable channels for distributing such a book--if the seed-oil industry can eliminate major corporate food products that have used coconut oil for a hundred years, they certainly have the power to prevent dealers from selling a book that would affect their market more seriously. For the present, I will just outline some of the virtues of coconut oil.

The unsaturated oils in some cooked foods become rancid in just a few hours, even at refrigerator temperatures, and are responsible for the stale taste of left-over foods. (Eating slightly stale food isn't particularly harmful, since the same oils, even when eaten absolutely fresh, will oxidize at a much higher rate once they are in the body, where they are heated and thoroughly mixed with an abundance of oxygen.) Coconut oil that has been kept at room temperature for a year has been tested for rancidity, and showed no evidence of it. Since we would expect the small percentage of unsaturated oils naturally contained in coconut oil to become rancid, it seems that the other (saturated) oils have an antioxidative effect: I suspect that the dilution keeps the unstable unsaturated fat molecules spatially separated from each other, so they can't interact in the destructive chain reactions that occur in other oils. To interrupt chain-reactions of oxidation is one of the functions of antioxidants, and it is possible that a sufficient quantity of coconut oil in the body has this function. It is well established that dietary coconut oil reduces our need for vitamin E, but I think its antioxidant role is more general than that, and that it has both direct and indirect antioxidant activities.

Coconut oil is unusually rich in short and medium chain fatty acids. Shorter chain length allows fatty acids to be metabolized without use of the carnitine transport system. Mildronate, which I discussed in an article on adaptogens, protects cells against stress partly by opposing the action of carnitine, and comparative studies showed that added carnitine had the opposite effect, promoting the oxidation of unsaturated fats during stress, and increasing oxidative damage to cells. I suspect that a

degree of saturation of the oxidative apparatus by short-chain fatty acids has a similar effect--that is, that these very soluble and mobile short-chain saturated fats have priority for oxidation, because they don't require carnitine transport into the mitochondrion, and that this will tend to inhibit oxidation of the unstable, peroxidizable unsaturated fatty acids.

When Albert Schweitzer operated his clinic in tropical Africa, he said it was many years before he saw any cases of cancer, and he believed that the appearance of cancer was caused by the change to the European type of diet. In the 1920s, German researchers showed that mice on a fat-free diet were practically free of cancer. Since then, many studies have demonstrated a very close association between consumption of unsaturated oils and the incidence of cancer.

Heart damage is easily produced in animals by feeding them linoleic acid; this "essential" fatty acid turned out to be the heart toxin in rape-seed oil. The addition of saturated fat to the experimental heart-toxic oil-rich diet protects against the damage to heart cells.

Immunosuppression was observed in patients who were being "nourished" by intravenous emulsions of "essential fatty acids," and as a result coconut oil is used as the basis for intravenous fat feeding, except in organ-transplant patients. For those patients, emulsions of unsaturated oils are used specifically for their immunosuppressive effects.

General aging, and especially aging of the brain, is increasingly seen as being closely associated with lipid peroxidation.

Several years ago I met an old couple, who were only a few years apart in age, but the wife looked many years younger than her doddering old husband. She was from the Philippines, and she remarked that she always had to cook two meals at the same time, because her husband couldn't adapt to her traditional food. Three times every day, she still prepared her food in coconut oil. Her apparent youth increased my interest in the effects of coconut oil.

In the 1960s, Hartroft and Porta gave an elegant argument for decreasing the ratio of unsaturated oil to saturated oil in the diet (and thus in the tissues). They showed that the "age pigment" is produced in proportion to the ratio of oxidants to antioxidants, multiplied by the ratio of unsaturated oils to saturated oils. More recently, a variety of studies have demonstrated that ultraviolet light induces peroxidation in unsaturated fats, but not saturated fats, and that this occurs in the skin as well as *in vitro*. Rabbit experiments, and studies of humans, showed that the amount of unsaturated oil in the diet strongly affects the rate at which aged, wrinkled skin develops. The unsaturated fat in the skin is a major

target for the aging and carcinogenic effects of ultraviolet light, though not necessarily the only one.

In the 1940s, farmers attempted to use cheap coconut oil for fattening their animals, but they found that it made them lean, active and hungry. For a few years, an antithyroid drug was found to make the livestock get fat while eating less food, but then it was found to be a strong carcinogen, and it also probably produced hypothyroidism in the people who ate the meat. By the late 1940s, it was found that the same antithyroid effect, causing animals to get fat without eating much food, could be achieved by using soy beans and corn as feed.

Later, an animal experiment fed diets that were low or high in total fat, and in different groups the fat was provided by pure coconut oil, or a pure unsaturated oil, or by various mixtures of the two oils. At the end of their lives, the animals' obesity increased directly in proportion to the ratio of unsaturated oil to coconut oil in their diet, and was not related to the total amount of fat they had consumed. That is, animals which ate just a little pure unsaturated oil were fat, and animals which ate a lot of coconut oil were lean.

In the 1930s, animals on a diet lacking the unsaturated fatty acids were found to be "hypermetabolic." Eating a "normal" diet, these animals were malnourished, and their skin condition was said to be caused by a "deficiency of essential fatty acids." But other researchers who were studying vitamin B_6 recognized the condition as a deficiency of that vitamin. They were able to cause the condition by feeding a fat-free diet, and to cure the condition by feeding a single B vitamin. The hypermetabolic animals simply needed a better diet than the "normal," fat-fed, cancer-prone animals did.

G. W. Crile and his wife found that the metabolic rate of people in Yucatan, where coconut is a staple food, averaged 25% higher than that of people in the United States. In a hot climate, the adaptive tendency is to have a lower metabolic rate, so it is clear that some factor is more than offsetting this expected effect of high environmental temperatures. The people there are lean, and recently it has been observed that the women there have none of the symptoms we commonly associate with the menopause.

By 1950, then, it was established that unsaturated fats suppress the metabolic rate, apparently creating hypothyroidism. Over the next few decades, the exact mechanisms of that metabolic damage were studied. Unsaturated fats damage the mitochondria, partly by suppressing the repiratory enzyme, and partly by causing generalized oxidative damage.

The more unsaturated the oils are, the more specifically they suppress tissue response to thyroid hormone, and transport of the hormone on the thyroid transport protein.

Plants evolved a variety of toxins designed to protect themselves from "predators," such as grazing animals. Seeds contain a variety of toxins, that seem to be specific for mammalian enzymes, and the seed oils themselves function to block proteolytic digestive enzymes in the stomach. The thyroid hormone is formed in the gland by the action of a proteolytic enzyme, and the unsaturated oils also inhibit that enzyme. Similar proteolytic enzymes involved in clot removal and phagocytosis appear to be similarly inhibited by these oils.

Just as metabolism is "activated" by consumption of coconut oil, which prevents the inhibiting effect of unsaturated oils, other inhibited processes, such as clot removal and phagocytosis, will probably tend to be restored by continuing use of coconut oil.

Brain tissue is very rich in complex forms of fats. The experiment (around 1978) in which pregnant mice were given diets containing either coconut oil or unsaturated oil showed that brain development was superior in the young mice whose mothers ate coconut oil. Because coconut oil supports thyroid function, and thyroid governs brain development, including myelination, the result might simply reflect the difference between normal and hypothyroid individuals. However, in 1980, experimenters demonstrated that young rats fed milk containing soy oil incorporated the oil directly into their brain cells, and had structurally abnormal brain cells as a result. Lipid peroxidation occurs during seizures, and antioxidants such as vitamin E have some anti-seizure activity. Currently, lipid peroxidation is being found to be involved in the nerve cell degeneration of Alzheimer's disease.

Various fractions of coconut oil are coming into use as "drugs," meaning that they are advertised as treatments for diseases. Butyric acid is used to treat cancer, lauric and myristic acids to treat virus infections, and mixtures of medium-chain fats are sold for weight loss. Purification undoubtedly increases certain effects, and results in profitable products, but in the absence of more precise knowledge, I think the whole natural product, used as a regular food, is the best way to protect health. The shorter-chain fatty acids have strong, unpleasant odors; for a couple of days after I ate a small amount of a medium-chain triglyceride mixture, my skin oil emitted a rank, goaty smell. Some people don't seem to have that reaction, and the benefits might outweigh the stink, but these things just haven't been in use long enough to know whether they are safe. We

have to remember that the arguments made for aspartame, monosodium glutamate, aspartic acid, and tryptophan--that they are like the amino acids that make up natural proteins--are dangerously false. In the case of amino acids, balance is everything. Aspartic and glutamic acids promote seizures and cause brain damage, and are intimately involved in the process of stress-induced brain aging, and tryptophan by itself is carcinogenic.

Treating any complex natural product as the drug industry does, as a raw material to be fractionated in the search for "drug" products, is risky, because the relevant knowledge isn't sought in the search for an association between a single chemical and a single disease.

While the toxic unsaturated paint-stock oils, especially safflower, soy, corn and linseed (flaxseed) oils, have been sold to the public precisely for their drug effects, all of their claimed benefits were false. When people become interested in coconut oil as a "health food," the huge seed-oil industry--operating through their shills--is likely to attack it as an "unproved drug."

While components of coconut oil have been found to have remarkable physiological effects (as antihistamines, antiinfectives/antiseptics, promoters of immunity, glucocorticoid antagonist, nontoxic anticancer agents, for example), I think it is important to avoid making any such claims for the natural coconut oil, because it very easily could be banned from the import market as a "new drug" which isn't "approved by the FDA." We have already seen how money and propaganda from the soy oil industry eliminated long-established products from the U.S. market. I saw people lose weight stably when they had the habit of eating large amounts of tortilla chips fried in coconut oil, but those chips disappeared when their producers were pressured into switching to other oils, in spite of the short shelf life that resulted in the need to add large amounts of preservatives. Oreo cookies, Ritz crackers, potato chip producers, and movie theater popcorn makers have experienced similar pressures.

The cholesterol-lowering fiasco for a long time centered on the ability of unsaturated oils to slightly lower serum cholesterol. For years, the mechanism of that action wasn't known, which should have suggested caution. Now, it seems that the effect is just one more toxic action, in which the liver defensively retains its cholesterol, rather than releasing it into the blood. Large scale human studies have provided overwhelming evidence that whenever drugs, including the unsaturated oils, were used to lower serum cholesterol, mortality increased, from a variety of causes

including accidents, but mainly from cancer. Since the 1930s, it has been clearly established that suppression of the thyroid raises serum cholesterol (while increasing mortality from infections, cancer, and heart disease), while restoring the thyroid hormone brings cholesterol down to normal. In this situation, however, thyroid isn't suppressing the synthesis of cholesterol, but rather is promoting its use to form hormones and bile salts. When the thyroid is functioning properly, the amount of cholesterol in the blood entering the ovary governs the amount of progesterone being produced by the ovary, and the same situation exists in all steroid-forming tissues, such as the adrenal glands and the brain. Progesterone and its precursor, pregnenolone, have a generalized protective function: antioxidant, anti-seizure, antitoxin, anti-spasm, anti-clot, anti-cancer, pro-memory, pro-myelination, pro-attention, etc. Any interference with the *formation* of cholesterol will interfere with all of these exceedingly important protective functions.

As far as the evidence goes, it suggests that coconut oil, added regularly to a balanced diet, lowers cholesterol to normal by promoting its conversion into pregnenolone. (The coconut family contains steroids that resemble pregnenolone, but these are probably mostly removed when the fresh oil is washed with water to remove the enzymes which would digest the oil.) Coconut-eating cultures in the tropics have consistently lower cholesterol than people in the U.S. Everyone that I know who uses coconut oil regularly happens to have cholesterol levels of about 160, while eating mainly cholesterol rich foods (eggs, milk, cheese, meat, shellfish). I encourage people to eat sweet fruits, rather than starches, if they want to increase their production of cholesterol, since fructose has that effect.

Many people see coconut oil in its hard, white state, and--as a result of their training watching television or going to medical school--associate it with the cholesterol-rich plaques in blood vessels. Those lesions in blood vessels are caused mostly by lipid peroxidation of unsaturated fats, and relate to stress, because adrenaline liberates fats from storage, and the lining of blood vessels is exposed to high concentrations of the blood-borne material. In the body, incidentally, the oil can't exist as a solid, since it liquefies at 76 degrees. (Incidentally, the viscosity of complex materials isn't a simple matter of averaging the viscosity of its component materials; cholesterol and saturated fats sometimes lower the viscosity of cell components.) Most of the images and metaphors relating to coconut oil and cholesterol that circulate in our culture are false and misleading. I offer a counter-image, which is

metaphorical, but it is true in that it relates to lipid peroxidation, which is profoundly important in our bodies. After a bottle of safflower oil has been opened a few times, a few drops that get smeared onto the outside of the bottle begin to get very sticky, and hard to wash off. This property is why it is a valued base for paints and varnishes, but this varnish is chemically closely related to the age pigment that forms "liver spots" on the skin, and similar lesions in the brain, heart, blood vessels, lenses of the eyes, etc. The image of "hard, white saturated coconut oil" isn't relevant to the oil's biological action, but the image of "sticky varnish-like easily oxidized unsaturated seed oils" is highly relevant to their toxicity.

The ability of some of the medium chain saturated fatty acids to inhibit the liver's formation of fat very likely synergizes with the pro-thyroid effect, in allowing energy to be used, rather than stored. When fat isn't formed from carbohydrate, the sugar is available for use, or for storage as glycogen. Therefore, shifting from unsaturated fats in foods to coconut oil involves several anti-stress processes, reducing our need for the adrenal hormones. Decreased blood sugar is a basic signal for the release of adrenal hormones. Unsaturated oil tends to lower the blood sugar in at least three basic ways. It damages mitochondria, causing respiration to be uncoupled from energy production, meaning that fuel is burned without useful effect. It suppresses the activity of the respiratory enzyme (directly, and through its anti-thyroid actions), decreasing the respiratory production of energy. And it tends to direct carbohydrate into fat production, making both stress and obesity more probable. For those of us who use coconut oil consistently, one of the most noticeable changes is the ability to go for several hours without eating, and to feel hungry without having symptoms of hypoglycemia.

One of the stylish ways to promote the use of unsaturated oils is to refer to their presence in "cell membranes," and to claim that they are essential for maintaining "membrane fluidity." As I have mentioned above, it is the ability of the unsaturated fats, and their breakdown products, to interfere with enzymes and transport proteins, which accounts for many of their toxic effects, so they definitely don't just harmlessly form "membranes." They probably bind to all proteins, and disrupt some of them, but for some reason their affinity for proteolytic and respiration-related enzymes is particularly obvious. (I think the chemistry of this association is going to give us some important insights into the nature of organisms. Metchnikof's model that I have discussed elsewhere might give us a picture of how those factors relate in growth, physiology, and aging.) Unsaturated fats are slightly more water-soluble

than fully saturated fats, and so they do have a greater tendency to concentrate at interfaces between water and fats or proteins, but there are relatively few places where these interfaces can be usefully and harmlessly occupied by unsaturated fats, and at a certain point, an excess becomes harmful. We don't want "membranes" forming where there shouldn't be membranes. The fluidity or viscosity of cell surfaces is an extremely complex subject, and the degree of viscosity has to be appropriate for the function of the cell. Interestingly, in some cells, such as the cells that line the air sacs of the lungs, cholesterol and one of the saturated fatty acids found in coconut oil can increase the fluidity of the cell surface.

In many cases, stressful conditions create structural disorder in cells. These influences have been called "chaotropic," or chaos-producing. In red blood cells, which have sometimes been wrongly described as "hemoglobin enclosed in a cell membrane," it has been known for a long time that lipid peroxidation of unsaturated fats weakens the cellular structure, causing the cells to be destroyed prematurely. Lipid peroxidation products are known to be "chaotropic," lowering the rigidity of regions of cells considered to be membranes. But the red blood cell is actually more like a sponge in structure, consisting of a "skeleton" of proteins, which (if not damaged by oxidation) can hold its shape, even when the hemoglobin has been removed. Oxidants damage the protein structure, and it is this structural damage which in turn increases the "fluidity" of the associated fats.

So, it is probably true that in many cases the liquid unsaturated oils do increase "membrane fluidity," but it is now clear that in at least some of those cases the "fluidity" corresponds to the chaos of a damaged cell protein structure. (N. V. Gorbunov, "Effect of structural modification of membrane proteins on lipid-protein interactions in the human erythrocyte membrane," *Bull. Exp. Biol. & Med. 116(11)*, 1364-67. 1993.

Although I had stopped using the unsaturated seed oils years ago, and supposed that I wasn't heavily saturated with toxic unsaturated fat, when I first used coconut oil I saw an immediate response, that convinced me my metabolism was chronically inhibited by something that was easily alleviated by "dilution" or molecular competition. I had put a tablespoonful of coconut oil on some rice I had for supper, and half an hour later while I was reading, I noticed I was breathing more deeply than normal. I saw that my skin was pink, and I found that my pulse was faster than normal--about 98, I think. After an hour or two, my pulse and breathing returned to normal. Every day for a couple of weeks I noticed

the same response while I was digesting a small amount of coconut oil, but gradually it didn't happen any more, and I increased my daily consumption of the oil to about an ounce. I kept eating the same foods as before (including a quart of ice cream every day), except that I added about 200 or 250 calories per day as coconut oil. Apparently the metabolic surges that happened at first were an indication that my body was compensating for an anti-thyroid substance by producing more thyroid hormone; when the coconut oil relieved the inhibition, I experienced a moment of slight hyperthyroidism, but after a time the inhibitor became less effective, and my body adjusted by producing slightly less thyroid hormone. But over the next few months, I saw that my weight was slowly and consistently decreasing. It had been steady at 185 pounds for 25 years, but over a period of six months it dropped to about 175 pounds. I found that eating more coconut oil lowered my weight another few pounds, and eating less caused it to increase.

The anti-obesity effect of coconut oil is clear in all of the animal studies, and in my friends who eat it regularly. It is now hard to get it in health food stores, since Hain stopped selling it. The Spectrum product looks and feels a little different to me, and I suppose the particular type of tree, region, and method of preparation can account for variations in the consistency and composition of the product. The unmodified natural oil is called "76 degree melt," since that is its natural melting temperature. One bottle from a health food store was labeled "natural coconut oil, 92% unsaturated oil," and it had the greasy consistency of old lard. I suspect that someone had confused palm oil (or something worse) with coconut oil, because it should be about 96% saturated fatty acids.

Recent Unsaturated Oil Research: References.

The following are some recent references I have seen that discuss the toxic effects of unsaturated fats, some of the things that offer protection against them., and some comparisons with saturated fats. I include a few references on the issue of "membrane fluidity," just to show that there is probably nothing of value in that idea.

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A LOGICAL DIET

Most diets are promoted for a single purpose, such as weight loss or heart protection, and usually they don't work even for a limited purpose. If a diet allows you to adapt to varied activities with a minimum of stress, it will help you to avoid many serious problems. Years ago, a retired dentist studied healthy people and their diets around the world, and found that many different diets supported good health, but when they began eating the "western" diet, based on grains, they quickly developed all the degenerative diseases.

There are some simple biochemical reasons for avoiding grains and beans, that I have discussed in more detail elsewhere. Plants put their most effective poisons into their seeds to protect their progeny. These toxins block digestive enzymes, lowering the food value of the material, but they also poison many other physiological processes--hormone production, immunity, and brain development, for example.

People who are accustomed to eating wheat shaped into dozens of foods that differ only in appearance and flavor sometimes say "there's nothing left to eat" if they eliminate grains, or stop relying on them for their main source of calories.

If we restrict ourselves mainly to animal proteins and low-starch fruits, we avoid the nutrient-poor foods, and still have an almost infinite variety of very pleasant foods. These foods are generally so rich in nutrients that a person could choose just a few of them, and be assured of an abundance of vitamins, minerals, and proteins.

Nutritional deficiency diseases probably wouldn't have been discovered if our diets hadn't been based on grains. The starches in grains aren't their only problem, but starch is uniquely suited to activate the formation of fat, and to stimulate appetite, especially an appetite for more carbohydrate, to restore the blood glucose that has been used up in making fat. Starch also has the ability to stimulate allergic responses, to plug small blood vessels and to accelerate aging (according to the work of G. Volkheimer, and others).

There is one form of grain that is relatively harmless because of the traditional method of processing it, and that is corn that has been made into tortillas or other native American foods, using alkali to detoxify it and make it more digestible. Pellagra was strongly associated with the use of ordinary corn, but not with the traditional preparations. Tortillas

fried in coconut oil and salted make a pleasant snack which is less nutritious than potato chips, but less allergenic and more digestible.

The sugars and minerals in fruits tend to stabilize the blood sugar, and when they are taken with protein foods, they allow the proteins to be used constructively, rather than being converted into energy. This combination minimizes the stress hormones, and promotes thyroid function, so that energy is available for use, rather than being stored as fat. For example, a glass of orange juice and an egg make a good breakfast, and cherries and cheese make a good snack. Chicken and watermelon, pineapple and ham, any combination of fruit and protein will make a balanced meal. Milk evolved as a complete food, according to this principle of combining sugar, protein, and minerals.

People who drink a quart of milk and a quart of orange juice every day are much less likely to have a hormonal imbalance than people who eat the average "well balanced" diet containing mostly vegetables, grains, and legumes.

One vegetable has a special place in a diet to balance the hormones, and that is the raw carrot. It is so nearly indigestible that, when it is well chewed or grated, it helps to stimulate the intestine and reduce the reabsorption of estrogen and the absorption of bacterial toxins. In these effects on the bowel, which improve hormonal balance, a carrot salad resembles antibiotic therapy, except that the carrot salad can be used every day for years without harmful side-effects. Many people find that daily use of the raw carrot eliminates their PMS, headaches, or allergies. The use of oil and vinegar as dressing intensifies the bowel-cleansing effect of the salad. Coconut oil is more germicidal and thyroid promoting than olive oil, but a mixture of coconut and olive oil improves the flavor. Lime juice, salt, cheese and meats can be used to vary the flavor.

CONCLUSION

Context is everything. The idea of balance--physiological, hormonal, or nutritional balance, for example--requires contextual thinking. Environmentalism is a form of contextual thinking. There are no closed systems, anywhere. Before the second world war, there were many influential people and institutions devoted to contextual thinking. With the rise of overwhelming corporate/state influence in the world, manipulative "public relations" has replaced critical thinking even, to a great extent, in the universities.

The main channels of communication are controlled by a few monopolies, which combine financial, weapons, pharmaceutical, agricultural, and energy interests in ways that are creating an interlocking set of almost rational-seeming beliefs. To orient yourself within this system requires some attention and effort, but once you perceive that your health and life are in the balance, it is usually possible to find the motivation and the energy to persist in critical, evidence-based thinking.

I have looked for the best workers in many scientific fields, and it seems that their discoveries fit into a meaningful picture of life. Warburg, Shute, Biskind, Lipschutz, Selye, Szent-Gyorgyi, Barnes, Ling, Meerson, and others have revolutionized biology and medicine, but their work has never supported the dominant corporate view, and so it has been actively suppressed by the forces that control science education.

The therapeutic methods that have grown out of their discoveries are simple, basic, inexpensive, and extremely effective.

NOTE: Some businesses have misleadingly used my name and parts of my research to imply that I support their products. The only formulation of progesterone that I approve is progesterone dissolved in vitamin E, and I hold the patent on that. It is useful when applied to the skin, but oral use is more economical. As this book explains, other solvents and additives can be harmful. Almond oil, avocado oil, safflower oil, etc., sensitize the skin to the aging effects of the sun, and are inappropriate for use on the skin or internally. Diosgenin, sometimes called wild yam extract, is toxic.

For information on my other books, newsletters, tapes, progesterone in vitamin E (2,850 mg. per ounce), coconut oil, etc., write to:
Raymond Peat, P.O. Box 5764, Eugene, Oregon 97405
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FROM PMS TO MENOPAUSE:
Female Hormones in Context

By Raymond Peat

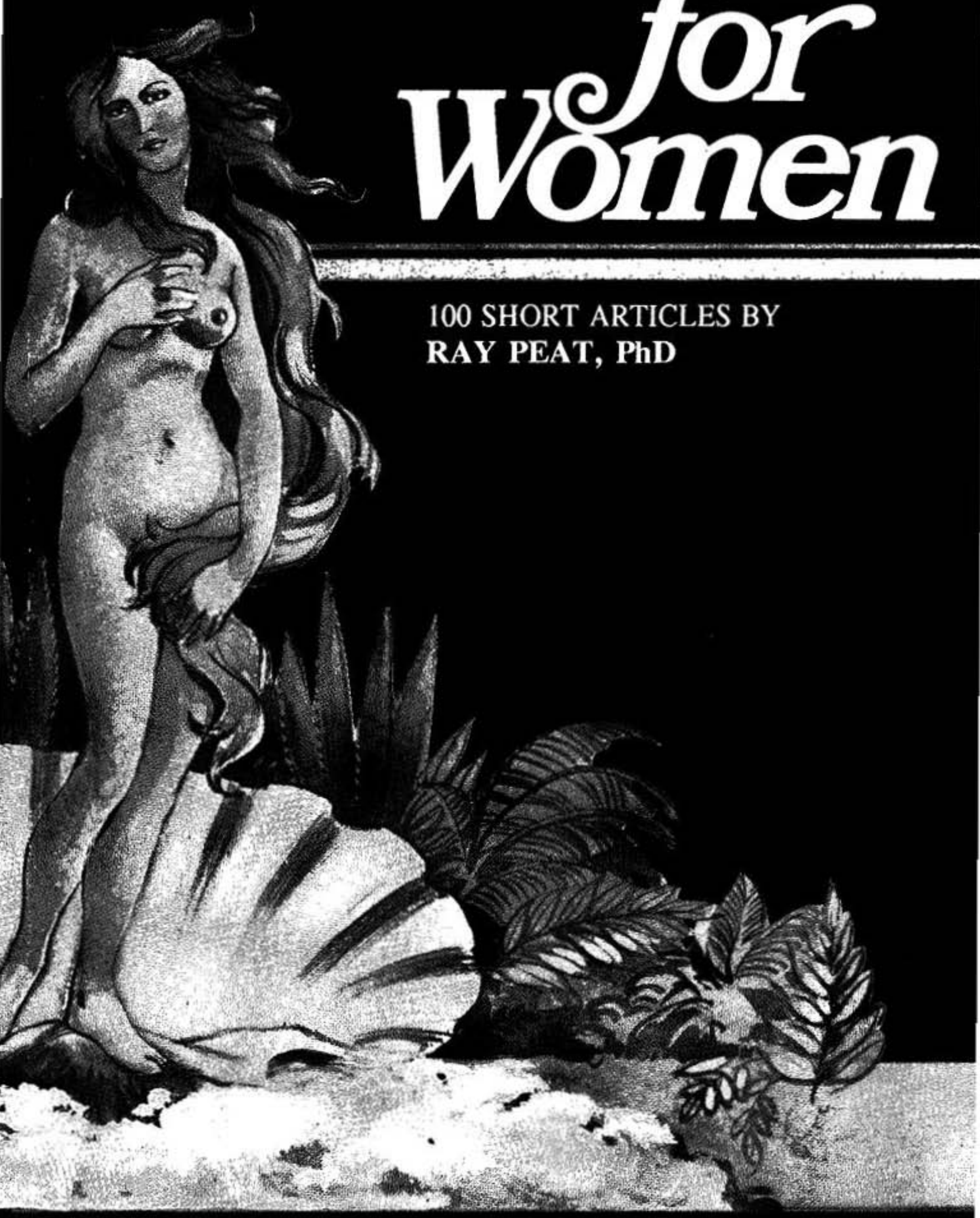
Many myths about female sexuality and health have been built into both medical education and popular culture. Understanding the subject scientifically means going against the current of both conventional medicine and alternative medicine.

To illustrate the roles of hormones and the various therapeutic approaches, a variety of problem areas, affecting women from childhood to old age, are considered in detail. For example, various sections focus on:

Eliminating migraine headaches
Alleviating the symptoms of menopause
Losing unwanted fat without "dieting"
Regulating fertility
Protecting pregnancy
Curing arthritis
Correcting nervous disorders

Raymond Peat received his PhD in Biology from the University of Oregon, specializing in physiology. He has written *Mind and Tissue, Progesterone in Orthomolecular Medicine, Generative Energy,* and *Nutrition for Women,* besides articles in journals. He has taught at the University of Oregon, Urbana College, Montana State University, National College of Naturopathic Medicine, Universidad Veracruzana, and the Universidad Autonoma del Estado de Mexico, and founded Blake College, International University. He does independent research and private endocrine and nutritional consulting.

Nutrition for Women



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Other books by Ray Peat:

Mind and Tissue

Progesterone in Orthomolecular Medicine

Generative Energy

INTRODUCTION

Occasionally, I read parts of this book to see whether I still agree with the orientation I had when I was writing it, and I see that it seems to be far enough ahead of the general culture that it has something useful for almost anyone. Rather than changing it, I will just add some new information that I have been concentrating on in recent years.

SALT

On page 90 I mentioned "too much salt" as a cause of water retention. That phrase was a lazy gesture recogni zing common medical opinion. If you suddenly increase your sodium intake, your body will take a day or two to adjust, and during that time you will retain a little extra water, but after the short adjustment time, you lose sodium at the same rate that you take it in. Under the influence of excess estrogen, your body retains extra water, and it is your appetite center which should balance that water by making you crave extra salt. If you learn to avoid salty foods at those times (or if you take a diuretic), your blood can't carry as much water as when it has enough salt, and so the salt stays in the tissues, rather than being carried to the kidneys. Tom Brewer demonstrated the importance of eating enough salt during pregnancy, to maintain adequate blood volume. When salt is restricted during pregnancy, the inadequate blood volume doesn't carry enough oxygen and food to the uterus to allow full development of the baby, and the kidneys secrete a hormone to increase the circulation, creating a tendency toward high blood pressure. Following Brewer's research, I saw that extra sodium should help in other situations involving circulatory inefficiency. Premenstrual edema, insomnia, and even high blood pressure often respond very well to a little extra

sodium in the diet. One of the most important effects of sodium is that it tends to spare magnesium, which is likely to be lost during stress and hypothyroidism. If we eat salty foods when we crave them, we are able to retain our magnesium more easily. Sodium also helps to regulate blood sugar, for example by improving its absorption from the intestine. There is even evidence that sodium can spare protein, since, if there isn't enough sodium to excrete into the urine to balance acids, the kidneys will waste protein to produce ammonium as an ionic substitute for sodium. But I think the most important point to remember is that it is essential for mainting adequate blood volume, and that it is almost always unphysiological and irrational to restrict sodium intake, because reduced blood volume tends to reduce the delivery of oxygen and nutrients to all tissues, leading to many problems. The emotional tension many people feel when they crave salt is, in some cases, the result of increased adrenalin, reflecting a real biological problem.

OBESITY

Several years ago, the death of a young physician from blood clots, while she was using a linseed oil supplement, caused me to realize the urgency of getting more information on the toxicity of unsaturated oils into an easily understandable form. While I was writing my dissertation, more than 20 years ago, I saw that there was already abundant research on their toxicity, but commercial propaganda for the "health benefits" of the "good unsaturated oils" (from seeds, nuts, and fish) had caused many people to overlook their harmful effects. At that time, it was clear that they promoted cancer, heart disease, and various degenerative diseases, and even premature aging. Agricultural research had demonstrated that they promoted obesity, and biochemists could

demonstrate a specific interence with our most essential respiratory enzymes. Although I knew of experiments in which rats grew fat according to the degree of unsaturation of the fats in their diet, regardless of quantity, and grew lean in proportion to the percentage of (relatively saturated) coconut oil in their diet, again regardless of quantity, I didn't get around to making practical use of these facts until I had spent several months reading the whole history of research on the biological effects of dietary fats.

The idea of "essential fatty acids" (sometimes called "vitamin F") appeared in the 1930s, as a result of tests in which rats developed a skin disease on a fat-free diet, and recovered from the skin disease when fed unsaturated fats. (Other researchers at that time observed that the rats became hypermetabolic on the fat-free diet, as though they were taking thyroid hormone; it was later discovered that the unsaturated fats inhibit the secretion and transport of thyroid hormones, and block the ability of tissues to respond to them.) Shortly after the concept of "essential fatty acids" was proposed, another group recognized the rats' skin disease as the typical changes produced by a vitamin B6 deficiency. They fed rats a fat-diet until the symptoms appeared, then cured the disease with a vitamin B6 supplement, without any of the supposedly essential fatty acids. The high metabolic rate of the rats, on a diet without the inhibitory oils, made them eat more, and they needed more vitamins as well as more calories. The high metabolic rate of animals fed coconut oil simply reflects the fact that coconut oil doesn't contain a toxic amount of the anti-thyroid, anti-respiratory unsaturated fatty acids.

Americans have a lower metabolic rate than some other cultures, and the result is that obesity is a major problem in this country. Since farmers had demonstrated that coconut oil (though it is cheap) was not good for fattening their animals--it made them lean and hungry--

and since cancer researchers showed it could lower the incidence of cancer, I began adding it to my diet. At first I noticed that I felt warmer after eating it, as if I had taken a thyroid supplement. Then I noticed that I was losing weight, while eating more calories than normal, because of adding about an ounce of coconut oil to my usual diet. After several months, I leveled off at a weight about 15 pounds lower than my "normal" weight of the previous 26 years. As some of friends learned what I was doing, they began eating coconut oil, with the same results. The biochemical basis seems clear: The easily oxidized short and medium-chain saturated fatty acids of coconut oil provide a source of energy that protects our tissues against the toxic inhibitory effects of the unsaturated fatty acids, and reduces their anti-thyroid effects. The animal studies of the last 60 years suggest that these effects also provide protection against cancer, heart disease, and premature aging. Other effects that can be expected include protection against excessive blood clotting, protection of the fetal brain, protection against various stress-induced problems including epilepsy, and some degree of protection against sun-damage of the skin.

While the use of coconut oil makes it possible to go longer without eating, because its pro-thyroid effect increases the liver's ability to store glycogen, frequent snacks are still important for helping to lose weight, or to prevent weight-gain. The mechanism is partly that smaller meals cause less insulin to be secreted, and insulin turns on the fat storage process, and increases appetite. Another important mechanism is that the liver provides about 70% of our active thyroid hormone, by converting thyroxine to T3, but it can provide this active hormone only when it has adequate glucose. Frequent snacks--for example, sipping a few ounces of orange juice about every hour--keeps the T3 level up by providing glucose to the liver. (Snacks shouldn't consist of protein by itself, since protein stimulates insulin, but not T3, secretion.)

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PREFACE

This book is intended for someone who already has questions about nutrition, or who feels insecure about the knowledge that is now available. I think it will answer many questions, while making you even more critical of the "official" attitudes toward health. Officially, women's nutritional requirements are not generally so different from men's. But all the special circumstances confronted by women in the U.S. haven't been considered by the compilers of official "Recommended Dietary Allowances." Some of these special circumstances that are important for women's nutrition are discussed here. with some general points that have sometimes been overlooked.

Since this book was published there has been a national conference on nutritional problems of women, and there have been articles and symposia on the nutritional effects of oral contraceptives. These "mainline" advances, however, still haven't caught up with the results of research. My recent additions to the book are intended to broaden the concept of nutrition and to direct attention to what I consider to be the most important problems and possibilities for women.

Delayed reproduction is one of the "newer conditions" leading to new physiological effects in many women. Disease patterns are changing, foods are changing, and the professions — with their normal 40 year lag between knowledge and application — are not able to deal with most of the new problems (they don't even deal too well with the *old* problems), so we have to become our own experts, learning how to find and evaluate useful information, to have an attitude of personal responsibility for knowledge as well as for action. The ideas in this book have been described by some as the physiological side of women's liberation, but of course there are political implications here too: why should we give privileged status to a profession which commits millions of unnecessary hysterectomies or which waits until the last quarter of the twentieth century to determine whether surgery is the best treatment for acute appendicitis (it isn't), or to the drug companies which fabricate their "safety and effectiveness studies" out of thin air, and then hire academic shills to promote their products, or to the food industry which adulterates and degrades our foods with the false excuse that this is required for economical mass distribution? Instead of giving them a privileged status, their criminal acts should be recognized and treated as such.

I. HORMONES

HORMONES AND PHYSICAL STATES: Suggestions, instructions, and possibilities for the improvement of life.

A. Estrogen and the organism.

When I have observed that estrogen does things to consciousness and behavior, as well as to the body, I have heard these responses: if you say submissiveness is hormonal you are setting the women's movement back a century; if estrogen interferes with memory, then why don't IQ tests show women to be less intelligent than men? and so on. First, I want to call attention to a hidden assumption, namely, that "biological is equivalent to genetic." That is not true, they are not equivalent, but geneticists have been remarkably effective in convincing the public, and the granting agencies, that biology is ultimately nothing more than genetics. A typical argument for that equivalence goes like this: "if you say that an organism is more than its DNA you are a Lamarckian, and possibly even a Stalinist, and those ideas were disapproved by Weismann, who cut the tails off several generations of mice and showed that it didn't influence the inheritance of tails." If you have fallen for that argument (which is repeated from grade school to graduate school), read Zamenhof and A.E. Needham (and their references) on the transgenerational effects of diet and environment. Genetics developed in a context of "social Darwinism", and still has an ideological bias: consider K. Lorenz and G. Stent.

Second, I want to point out that men produce estrogen, especially under stress such as starvation or alcoholism or liver damage. In a famine, men may even lactate. Third, on the question of IQ tests, Dalton has shown that women who are suffering from an excess of estrogen do worse in both mental and physical performance than when their hormones are in balance. Women are not distinguished from men only by having more estrogen, as many people (including doctors) seem to believe. Quantitatively, progesterone is the main female hormone, and progesterone improves brain structure and function. The primary male hormone, testosterone, has chemical and functional properties of both estrogen and progesterone; this combined function gives males a short-term stability (fewer goiters, migraines, etc.) but a lack of adaptiveness in the longer range (higher mortality in infancy and old age). The placenta is a central factor in the development of the brain, but there is very little known about possible differences between males' and

females' placentas, and their effects on such things as the greater mortality of male fetuses and the greater variability of males' intelligence.

Estrogen does block memory, according to animal studies as well as clinical experience: many of the women I see (especially if they have used birth control pills, have had special social problems, have eaten a vegetarian or soybean-rich diet, and if they have lived in a cloudy region) have very poor memory and a "foggy feeling in their head." High estrogen during pregnancy causes fetal brain damage and retardation. Too much unsaturated vegetable oil during pregnancy has the same effect. Both of these interfere with energy production: wasting oxygen, altering the effects of thyroid hormones, etc.

Estrogen is the hormone for beginnings, a sort of biochemical eraser which can eliminate recently recorded information, restoring the underlying primitive capacity for growth. When we are threatened, by injury or aging, we need the capacity for renewal of cells. Estrogen promotes production of prolactin, a protein hormone, and its close analog, growth hormone. Ionizing radiation, aging, and oxygen deprivation all cause biochemical changes similar to those produced by estrogen. Excessive estrogen (and the prolactin excess it induces) can be dangerous. A few biologists are talking about a "death hormone" which appears in the pituitary at puberty — I suspect prolactin (or another estrogen-induced peptide) is the hormone producing the effects they see. In salamanders, prolactin initiates the process of limb regeneration. Various cancers depend on estrogen and prolactin. A variety of substances promote tumefaction, lump formation, growth without differentiation. Rather than being hormones of death, I think of these as "renewal hormones," hormones of potential immortality. Anything which produces tissue atrophy will tend to produce cancer. The important question is, what will induce differentiation and useful function in cancer cells? There are many substances which promote differentiation and oppose the effects of estrogen, and some of these have been found to be useful in cancer therapy. Among the substances opposing estrogen are dopamine and nickel, prolactin inhibitors; chalones, the tissue specific proteins which inhibit cell division (and possibly more ephemerally, the peptides of memory); the aprotic solvents, DMF and possibly DMSO; progesterone and testosterone; thyroxin and iodine; magnesium ATP, the stable form of the "biological energy" molecule; vitamin A, a protein-sparing nutrient which promotes differentiation, and vitamin E (and the closely related coenzyme Q, or ubiquinone).

B. Organism and environment.

What does it mean to be biologically integrated with our environment, or with our experiences of it? For one thing, it *doesn't* imply a closed perfect timeless system; everything evolves. We have enough integration and consistency that we can survive, but an essential feature of the environment is that it is open and unlimited. When our environment shrinks, when there isn't enough food, we can adapt, for example by replacing muscle with fat and by having small-brained babies (the brain is an expensive organ, energetically, though its efficiency increases with its expense). When our environment meets our needs our brains and muscles expand. The lower leg (like the brain) is a good indicator of environmental support: parents who grew up in a population which has atrophied-looking lower legs can have children with beautifully developed legs, when milk becomes abundantly available. Boas (1912) recorded first generation changes in head shape in the children of immigrants. Brain size is likewise very rapidly increased with a good diet (or, in rats at least, with a more interesting life).

The brain (and especially its frontal tissue) is like a window onto both present and past environments. It saves as much as it can of past environments, but particularly, it saves those aspects of the environment which seem favorable, which hint at abundance and possibility. The frontal lobes of the brain are like the mainspring of a clock: in "hyperkinetic" people, in some psychotic and some lobotomized people, the mainspring — the energy storing system — is broken or weak: the clock will tick only when shaken. The individual with a defective mental energy storage system might dash around keeping his mind stimulated, or it might be that coffee or other nerve stimulants will raise the level of energy to the point that quiet integration becomes possible. The persistence of attention from one situation to another makes generalization and discovery possible. Given a favorable environment, the passage of time leads to the accumulation of awareness, to the discovery of new aspects of the environment, new ways of living; it leads to doing things more intelligently.

This can be said in physical and biochemical terms: if a shrinking environment doesn't interfere, the passage of time leads to a brain state which is both more energetic and more efficient. Vital stains show that these energetic changes go with structural changes in the cytoplasm, such that high energy efficient metabolism occurs when the cytoplasm has affinity for oily dyes. When water is at a surface it is ordered or structured so that it loses much of its wetness; a bug can walk on it; it contains more heat (or is colder for a given

amount of heat). Water is unusual in its capacity for internal structural modification, and for its heat capacity. During cell division, muscle contraction, and nerve stimulation, there is a release of heat (followed by an uptake of heat as the muscle or nerve recovers) which cannot be accounted for by any known *chemical* change. Its order decreases with increasing temperature, unless order is introduced by other substances. (The brain has used and exaggerated these properties of water.) Biological and environmental influences can modify these substances so that the cell water undergoes a "phase transition," analogous to the melting of ice. Muscle contraction, nerve conduction, synthetic and secretory activity, etc., appear to be regulated by these phase changes. Cooperative, or holistic, changes of cells and tissues are easier to understand from this integrated point of view, than from the conventional molecular and atomistic viewpoint.

These changes in the "solvent," or the intracellular medium, will alter chemical reactions — by modifying enzymes and by "sequestering" classes of chemicals, much as the aprotic solvents, DMF and DMSO, speed and alter reactivity. Following these "solvent" changes, we should expect the chemical consequences to amplify or "institutionalize" those changes. For example, proteins could be modified to produce appropriate patterns of "memory molecules" and "endorphins" (protein fragments having actions similar to morphine) and chalones. Patterns of excitation become stabilized as knowledge, and as developmental modifications of tissue: growth and aging and their ramifications. An excess of estrogen, or other factors interfering with proteolysis, could block the capacity to experience. The difficulty of recalling dreams probably relates to this synthetic (non-proteolytic) parasympathetic dominance during sleep.

The accumulation of aspects of the environment in our tissue, modifying our tissue's functioning and its affinity for various substances, is a short-time analog for the general upward drift of evolution, and it has presently known and distinct links with inheritance: hormonal influences pass both ways across the placenta, and maternal efficiency determines the supply of nutrients — e.g., sugar — to the fetus. "Lingering modifications," transgenerational influences of the environment, are visible in a great variety of organisms and organs, but it is in the brain — the environmental organ — that these Lamarckian effects are so visible and so crucial. If we think of the organism as an accumulation of its past environments, we must keep in mind that the accumulation is always occurring as the residue of the past strives to grasp (and to form) new environments. We do not willingly enter and conform ourselves to an undesirable environment.

C. Stress and politics.

Stress will cause a rise in estrogen, and a loss of anti-estrogens such as thyroid, progesterone, and (in men) testosterone. Male apes who are bullied have decreased levels of testosterone, and this effect persists long after their environment has improved. The stress of subjugation seems to lead to an adaptation of passivity. Their passivity prevents further injury, but we don't know how stressful their continuing submission is. Hans Selye found that the adrenals are a major component of our adaptive system. In the first phase of stress, there is a shock reaction (with changes resembling those of estrogen dominance), with injury to various tissues. In the second phase, the adrenals protect the animal, and this protection continues until something is exhausted. By exposing rats to a preliminary stress, Selye found that he could induce adaptation to other, later stresses — a kind of immunization to stress. About 1957, psychologists noticed that a rat could "learn helplessness": if they held a rat until it stopped struggling, it would then die much sooner than a normal rat does when put into a barrel of water. They also found that they could "immunize" their rats against learned helplessness, by previously allowing them to experience success in a similar situation. The short-term learned helplessness apparently does something to block the efficient use of energy, so that the animal dies of exhaustion very easily, i.e., it has depleted one source of energy without mobilizing another.

Energetically, the estrogen-dominated metabolic state is less efficient than the oxidative state which is dominated by thyroid and progesterone (or testosterone). The estrogen state, like the rats' state of learned helplessness, is "parasympathetic," in the sense that many chemical balances have moved away from the mobilized "sympathetic" or adrenergic state. The estrogen state, for example, depresses blood sugar, while the mobilized state spares glucose by oxidizing fat.

Since the rats can be "immunized" against becoming helpless during restraint, by previously experiencing success, it seems that something more is involved than Selye's pre-conditioning. It seems to be the *meaning* of the particular experience of restraint that affects the animals' capacity to struggle. The perception of possibility, of a vista that extends convincingly toward a better future life, seems to modify the metabolic apparatus. Drowning rats, it happens, will drown before they discover the liberating possibilities. Successful struggle takes a *little* while to get organized. I suspect that life in a rat-box was an essential factor in those experiments, and that a life of reasonable opportunity would prevent such learning of helplessness.

Men can be habitually passive. and can also have an excess of estrogen, so I am not implying (when I talk about the estrogenic state) either that the male sex is necessarily the source of human oppression nor that women invite their own subjugation by a hormonal predisposition. I do want to suggest that the hormonal conditions for easy subjugation are alterable, within the individual. from generation to generation and that better social conditions can improve our physiologies. High estrogen traits can be both acquired and passed on to offspring, as discovered by L.C. Strong in his mice, and as confirmed recently in rats that were stressed during pregancy. I also want to point out that, within some privileged classes. women as well as men seem to actively promote their own role of passivity, relative to their men, probably because they sense that their position (and their children's) is threatened by widespread social and sexual change. Of course, men of *various* classes also encourage their women to be dependent, but my point is that historical and class processes are involved, and must be understood by those who want to improve human relationships. J.W. Prescott showed that, in all the societies he investigated, an inferior status for women was associated with sexual repression. self-mutilation, mystical-religious attitudes, militarism, and a hierarchical class system. Prescott suggests a two-state system in the brain, such that people do all those unpleasant things when they grow up deprived of pleasure. Interestingly, forty years earlier J.D. Unwin, a Freudian anthropologist who (unlike Prescott) favored repression, militarism, etc., came to the same conclusions. Behavior affects the hormones, and hormones influence behavior. Life in a rat-box society makes brains grow smaller, and makes people do the things that maintain the oppressive conditions. Nutritional and hormonal social intervention can change this.

D. Pleasure and hormones.

The first time I took enough desiccated thyroid to make my heart speed noticeably, there was a pleasure pushing up from my abdomen through my chest. making me want to smile and laugh. When I have watched suicidal women using thyroid or progesterone, there is a transformation (under an hour with progesterone, a few hours or longer with thyroid) from weeping to smiling and laughing; they speak of unbearable pain being replaced by pleasure. Women who have had orgasms while taking thyroid have lost their sexual responsiveness when they stopped. A woman said, soon after she began using progesterone and thyroid, that, for the first time in her life she felt that her heart and abdomen were

opening with feelings of love. Another said "thyroid is love." Since these women were using the hormones for problems that had developed gradually, over several years if not their entire life, the sudden change was dramatic. They had forgotten that life itself was pleasurable. Our culture doesn't explicitly teach us that life is pleasureless, though it does make life pleasureless for many, and it does teach that pleasure is worth less than virtue, utility, possession, etc. By improving life conditions (in many ways) the hormones of pleasure can have a bigger role in our physiology. I think the experience of pleasure (whatever capacity for pleasure there is) increases the ability to experience pleasure, but I don't offer this with much hope as a therapeutic approach, since I know of people who say that running to exhaustion makes them "feel good" — neither "feeling good" nor "having orgasms" has a clear meaning, at present.

E. Nutrition and brains.

In regions where most people die before the age of five, those who do grow up are severely malnourished, and have brains that are much smaller than normal. Studies in Latin America have compared brain size and neurological development in villages eating "normally," and in nearby villages in which pregnant women and babies received a small nutritional supplement, and have shown that head size (and mental development) can be increased by a little improvement in the diet. Animal experiments, as well as a recent study of Americans, show that this improvement could be cumulative, if continued into the next generations.

Additionally, when the mothers' general health is so poor that nutrition just during pregnancy can't overcome the lifelong deprivation, the use of hormones could keep the mother in good health during pregnancy, and act as a buffer between the fetus and the mother's metabolic instability. In some areas, thyroid hormone would be crucial. In every area, for a large percentage of women, progesterone can improve gestation. Thyroid supplementation would cost only about $2 per pregnancy, progesterone would cost from $2 to $15. The difference between a passive person with an 85 IQ and an independent person with a 130 IQ is very great; if all the children in a village could be so healthy, many aspects of the society would change. I suppose this explains why none of the people who give money for research or humanitarian projects has been interested in supporting such a project. With adequate support, many foods could be evaluated for their effect, positive or negative, on gestation and brain development.

There is a medical myth about large-headed babies

being hard to deliver. When the pelvis is seriously deformed, there is a problem, but the fact is that very large babies are delivered with great ease when the mother is in good health, because the factors which support growth of the baby also promote elasticity of the mother's tissues. Progesterone is such a factor — almost a "chemical obstetrician."

It has been observed that the ratio of brain weight to body weight corresponds directly to longevity. The brain has a nourishing, trophic influence on other tissues. A stable, efficient brain is an anti-stress agent. The hormones of stress age various tissues, including the brain, and the collagen in connective tissue. Good nutrition, including the anti-stress substances found in certain foods, will simultaneously optimize intelligence and increase the healthy life-span. Congenital defects are increased by stress and poor nutrition during pregnancy, and reduced by good nutrition, hormone supplementation, and stress reduction. Even in rich cultures, protein deficiency, inappropriate exercise, and emotional tension will contribute to premature aging of the individual, and damage to the offspring.

F. Long-range order.

There is a continuity from the molecular level through our physiological states into our way of life. The properties of water, modified by biological substances and biological experience, allow a kind of physiological (and epistemological) unity which is unimaginable for the atomistic genetic determinists. The existence of long-range order in a liquid is now respectable, because liquid crystals are in common use for watch dials and calculator display devices. Long-range order is a principle of biological thinking which brings us into a new phase of theory. Succeeding in biology, this principle can help us to re-evaluate other events in the history of ideas about physical state. For example, it is now clear that Polanyi's adsorption potential was a fact, and Einstein and Haber were dogmatically wrong in their ideas about inter-atomic forces. Seeing this, we should question the many consequences of the same mistaken atomistic view, including Einstein's theory of photoelectricity, which attributed a corpuscular quality to light, because he "knew" that matter was strictly particulate without any of the long-range energy properties that were later demonstrated by Polanyi.

Biology is now approaching a time when it will be increasingly frustrated by the inability of chemists and physicists to think clearly about the assumptions they have

made. A few physical scientists have begun to realize that concepts developed in biology can solve problems in, for example, the physics of absorption. Thinking about life, our assumptions should be fewer and less arbitrary than in simple sciences.

When we speak about "our mental state and our physical state," we may eventually achieve the concreteness and generality which a physicist has in describing, e.g., "the solid state," but this will be an expansion of physics, not a reduction of biology.

WHY PRESCRIBE ESTROGEN?

Millions of women with already high estrogen levels are being sold estrogen pills or injections, often prescribed as treatment for symptoms known to result from excess estrogen. When this treatment fails, and symptoms get worse, a tranquilizer is often added to the treatment. Surgery frequently follows. Many healthy wombs are removed as a "preventive" measure. I have talked to many women who have been ravaged by this kind of medical treatment; asking them how their "low estrogen" had been diagnosed, they say "by a Pap smear," or "he could tell by looking at my eyes," or even vaguer methods. I have only talked to one woman who had her blood estrogen level actually measured.

Controlled scientific studies don't play much of a role in the practice of medicine. This widespread use of estrogen is not only unsupported by such valid studies, but is in opposition to most of the real data that exist. Foreign physicians have asked how it was possible to speak of "hormone replacement therapy," when the estrogen level in the blood was often maintained at 1000 percent of normal.

Hepatitis and other liver problems are known to be increasing. Women's livers are known to be more sluggish than men's in removing chemicals from the body. When the liver doesn't remove estrogen from the body rapidly enough, estrogen accumulates in the body — this is why male alcoholics often grow breasts. Estrogen pills and tranquilizers add to the liver's burden. Poor nutrition makes it impossible for the liver to function properly.

It has been known for several decades that many of the symptoms of hormone imbalance can be relieved with simple nutritional therapy. If doctors don't want to take the time to study the literature, they should at least be referred to one of the simply written articles, such as Biskind's on the liver and hormones in *Vitamins and Hormones,* 1946.

SOME SYMPTOMS OF ESTROGEN EXCESS

In a recent nutrition class, a young woman who prepared nutritionally perfect meals (even exceeding the established "recommended daily allowances") was getting ready to have breast surgery, because for two years she had had painful cysts. One of the things we discussed was a 1946 paper by Biskind on estrogen and the liver, in which it was pointed out that a B vitamin deficiency slows the liver's elimination of estrogen, so that it accumulates in the body, producing a series of classical symptoms, including cystic mastitis.

During the course, we had also discussed how vitamin A can often benefit secretory tissues, such as the glands which maintain hormonal balance.

The last day of class, she told me that, for the first time in two years she had no breast pain, and her doctor had told her she was completely free of the cystic condition, and called off the surgery.

The other symptoms mentioned by Biskind include adrenal cortex hypertrophy, uterine bleeding, premenstrual tension, diminished libido and impotence in the male, and cutaneous vascular spiders. He mentions that the diminished testicular function of diabetes can be improved by nutrition, as can an enlarged liver, and that PABA sometimes improves the libido. He wrote that thiamine and riboflavin seemed to be responsible for the liver's regulation of estrogen, but that the amino acid methionine was also essential. Lipschuts (Steroids and Tumors, 1950) reported that protein is crucial for estrogen removal. Recent studies in monkeys show that menstruation is brought on when the progesterone level falls and the uterine blood vessels dilate, then go into spasm. Many of the symptoms of estrogen excess are equivalent to those of a progesterone deficiency. Progesterone is a direct antagonist of estrogen; Lipschuts (and Korenchevsky) have shown that progesterone causes regression of tumors induced by estrogen. Thyroid hormone and Vitamin A promote protein metabolism and antagonize some of estrogen's effects. In fact, hyperthyroidism is known to be able to cause estrogen levels to fall below normal. Vitamins C and E are also known to help the liver deal with toxins. Puffiness, usually most noticeable in the face in the morning and the feet at night, is another common symptom of estrogen excess, caused by the retention of water and sodium.

ESTROGEN AND SEX

Masters, the sex researcher, recently mentioned that quite a few women have been losing their ability to have an orgasm after being on the pill for 18 months or longer, and

that they are also losing their interest in sex, or their ability to be aroused easily. Since this doesn't happen to everyone, and takes a fairly long time to develop, we can probably understand it best by considering other effects of the pill that develop slowly. It's well known that taking estrogen can cause the blood to clot too easily. Other effects include anemia, low blood sugar, and slow functioning of the liver.

Some people will say that the pill inhibits estrogen production, and that the loss of sex interest means that these women need more estrogen. However, the other effects produced by the pill are pretty clearly the result of an excess of estrogen, at least in relation to other hormones, and I think it might be dangerous to increase the dosage of estrogen hoping to restore normal sexual function.

Normally, the liver treats estrogen like a poison, removing it immediately from the body. If the liver gets sluggish from malnutrition or too much estrogen (or other damage), it can allow the hormone to build up to very high levels. Since estrogen is metabolically antagonistic to progesterone and testosterone, I think the pill might decrease libido by counteracting these other hormones. They raise the energy charge of cells, and contribute to a sense of well-being. Testosterone stimulates sexual desire in both sexes. The energy charge of cells can govern nerve reflexes, and so I think it is reasonable to suppose that the quality of sexual arousal and orgasm could be influenced by the relative balance of estrogen and progesterone or testosterone.

An I.U.D. (intra-uterine contraceptive device) is known to be "luteolytic", meaning it suppresses progesterone formation and leads to a relative excess of estrogen. This suggests that I.U.D.s might also eventually make it hard to have orgasms. Copper seems to be synergic with estrogen, and could have a similar effect — could this have something to do with the de-emphasis of sex among some vegetarians who eat lots of copper-rich soy beans? Copper I.U.D's would seem the most likely kind to interfere with sexual satisfaction.

My impression (from women I have known) is that excessive estrogen will first produce little orgasms, with a need to have many in succession. The low blood sugar resulting from high estrogen can cause depression, irritability and sleep problems. When a lower ratio of estrogen to the other hormones exists, I think the pattern is more likely to be one large, intense orgasm followed by sleep, with the next arousal not coming for about 1 and one half hours.

If a person (especially, though not necessarily, a woman) has unsatisfying orgasms, or no orgasms at all, I think it would be advisable to eliminate the possible causes of a hormone imbalance (including high copper intake), and also to help the liver function as effectively as possible by getting good nutrition. High protein, all the B vitamins,

vitamins A,C, and E, and zinc and magnesium are especially important. Vitamin E does several things biochemically which are exactly the opposite of what estrogen does, so it has been called the "anti-estrogenic vitamin."

Magnesium has a very powerful sedative — even anesthetic — effect, which seems to be especially favorable to healthy sexuality. I suspect that it will eventually be known as an "anti-estrogenic mineral," and, with zinc, may turn out to be effective in a wide variety of sex-related problems. It is already a traditional therapy for prostatitis. Male impotence as well as female sex problems can sometimes benefit from special nutrition.

According to S. Zuckerman (1955), excess estrogen causes enlargement of the prostate in dogs. More recent studies have used progestins to relieve prostate enlargement in men. These observations suggest that excess estrogen may be a frequent factor in male sexual problems. I now suspect low thyroid is a factor in most such cases, and advise the elimination of nuts, beans, broccoli, corn oil, and other thyroid inhibitors from the diet.

VITAMIN E AND SEX

In another section on estrogen, I mention that too much estrogen seems to interfere with sexual responsiveness and orgasm, and I suggested that a tendency to have a series of small or only partly satisfying orgasms could result from an excess of either estrogen or copper, since copper and estrogen have some biochemical similarities and interactions. While zinc can counteract copper, many of the effects of estrogen can be offset by vitamin E. (Vitamin C can also detoxify and help to excrete metals.)

Estrogen seems to increase the body's need for vitamin E, as it does for many other nutrients. Pregnancy, which can leave the woman with an elevated estrogen level, seems to raise the amount of vitamin E needed to sustain the following pregnancy, if we can generalize from animal experiments. During the first year of a rat's life, the amount of vitamin E needed to sustain pregnancy increases by about 65 times (J. of Clinical Nutrition, Sept. 1974).

Just as too much estrogen causes sterility, it seems that it can also cause loss of sexual "capacity". Since vitamin E can often restore fertility (e.g., E.V. Shute, J. Endocr. 2, p.173, 1940), it is likely that it can also sometimes restore the libido.

Newborn rodents often respond to stimulation with the behavior of a mature female in heat, and this doesn't seem to be produced by estrogen. Rather, it seems to be produced by the slight oxygen deprivation at birth. My own experiments have shown that vitamin E tends to raise the oxygen content

of tissues, at least when the tissue is under the influence of estrogen. I suspect that estrogen acts largely through its effect on oxygen metabolism — a sort of biochemical breath-holding. For certain nerve systems, both taking vitamin E and having an orgasm might be compared to taking a good deep breath.

To continue the analogy between breathing and orgasm, having an orgasm without enough vitamin E would be like sneezing without first inhaling. Some people really do this, and the effect is a series of very small, quick sneezes. That is, if the nerve-muscle system can't get into the "ready state," the tension can't resolve itself normally. (This "ready state" of the tissues has been studied in the Soviet Union more than in the U.S.; I describe these studies in my book *Mind and Tissue*).

Vitamin E preserves ATP. ATP is a source of biological energy, but it also stabilizes or relaxes tissue. This energized relaxation is the "ready state." In a dead animal, ATP disappears from the tissues and the muscles contract and harden, but if ATP is injected the muscles will become soft again. In a vitamin E deficiency, certain tissues lose enough ATP that they can't function normally. Muscles cramp, and eventually can harden and become dystrophic. Magnesium also helps to maintain ATP levels, and for example can be used to stop menstrual cramps. In an extreme case of vitamin E deficiency, reflexes become abnormal; in some animals, softening of the brain is the first symptom of a vitamin E deficiency.

The highest part of the brain, in evolution, is the expectancy/planning system in the frontal lobes. Delayed and appropriate response is impossible if these lobes don't function well. In a healthy animal, arousal means expectation: the longer arousal can be sustained without distraction, the higher the energy charge will be, and the more intense and satisfying the completion will be.

Trying to sustain excitement too long, for example while waiting for your partner to finish an elaborate preparatory ritual, can exhaust the desire, the emotion and tension; the expectancy pattern fades. Losing sleep, or getting too hungry can have the same effect by causing low blood sugar. The brain needs a large supply of glucose to function well. Incidentally, oversleeping can cause the blood sugar to fall. High estrogen can also cause low blood sugar.

People have always suspected that sexual desire was part of the highest human functioning. The expectancy process in the most uniquely human part of the brain is as essential for good sex as it is for good art or good science. Adequate nutrition, including vitamin E, is extremely important for the full functioning of this system.

ESTROGEN AND THYROID: A NOTE FOR PHYSICIANS

The idea of physiological compensation is sometimes overlooked in interpreting endocrine interactions, with confusing results. The brain-pituitary system (not just the hypothalamus, since the whole brain and sensory system participates as "reflex setter") is probably the main regulatory or compensating system. If estrogen is injected into an animal, the level of thyroid stimulating hormone rises (Brown-Grant, *J. Endocr. 35,* 263, 1966). This should be taken as a hint that the peripheral effect of estrogen can be compensated for by thyroxin. If thyroid functioning is borderline, it would also suggest that elevated estrogen might be uncompensated peripherally. There are many known examples of metabolic or functional opposition of estrogen and thyroid.

Blood Sugar

Estrogen lowers blood sugar by stimulating insulin release (Goodman and Hazelwood, *J. Endocr. 62,* 439, 1974), and also apparently by blocking the synthesis of andrenal corticoids (Turner, *General Endocrinology,* Sanders Co., Phila., 1966), while thyroxin raises blood sugar (Turner, ibid.).

Fat Synthesis/Lipolysis

Synthesis of lipids is promoted by estrogen (Peat and Soderwall, *Physiol. Chem. and Physics 4(3),* 295, 1972), while thyroxin promotes lipolysis possibly acting through adrenalin (Turner, op. cit.).

Liver Catalase Activity

Reflecting an altered respiratory pattern, liver catalase activity seems to be lowered by estrogen (Adams, *J. Reprod. Fertil. 12,* 9, 1970) and raised by thyroxin.

Proliferative Response of Lymphoid Organs

The proliferative response of lymphoid organs, measured as the rate of DNA synthesis, is increased by estrogen or insulin and decreased by thyrotropin (Maor, *et al., Acta Endocrinol. 75(1),* 205, 1974).

Size of Thymus

Apparently thymolysis is blocked by thyroxine, and promoted by estrogen (stress, radiation and starvation also cause thymus shrinkage).

Lactation

Starvation and injection of estradiol both suppress lactation while thyroxine injection stimulates lactation (Oshima, *Bull, Natl. Inst. Anim. Ind (Chibal) 26*, 45, 1973).

Opposing effects of these hormones are also seen in fever and thermogenesis, in fertility (Peat, dissertation Univ. of Oregon 1972; Harrison et al., *Principles of Internal Medicine*, 1950), and in methionine metabolism (Finkelstein and Harris, *Arch. Biochem. Biophys. 159 (1)*, 160, 1973). Brown-Grant, *J. Physiol. 176*, 91, 1965) has commented on the idea of compensatory cycling of thyroid activity: "... the sudden drop in thyroid activity during metoestrus amd dioestrus could well be a compensatory decline below the mean level, resulting from the release of an excess of hormone above the needs of the animal during oestrus." The data showing peripheral opposition of the hormones suggest that the need for thyroxine varies with the estrogen cycle. The fact that myxedema is 5 times more frequent in females (adult) than male also suggests such an effect of estrogen (Harrison, *op. cit.*, p. 611). Water and sodium retention induced by estrogen (Korenchevsky, *Physiol. and Pathol. Aging*, Hafner, N.Y. 1961) may be hard to distinguish from the water retention of myxedema. Iodine, protein and electrolyte balance should be given special attention in women who may have an estrogen imbalance.

THYROID

Thyroid hormone is necessary for respiration on the cellular level, and makes possible *all higher biological functions*. Without the metabolic efficiency which is promoted by thyroid hormone, life couldn't get much beyond the single-cell stage. Without adequate thyroid, we become sluggish, clumsy, cold, anemic, and subject to infections, heart disease, headaches, cancer, and many other diseases, and seem to be prematurely aged, because none of our tissues can function normally. Besides providing the respiratory energy which is essential to life, thyroid hormones seem to stimulate and direct protein synthesis.

In hypothyroidism there is little stomach acid, and other digestive juices (and even intestinal movement) are inadequate, so gas and constipation are common. Foods aren't assimilated well, so even on a seemingly adequate diet there is "internal malnutrition." Magnesium is poorly absorbed, and a magnesium deficiency can lead to irritability, blood clots, vascular spasms and angina pectoris, and many other problems. Heart attacks, hardening of the arteries, and both high and low blood pressure can by caused by hypo-

thyroidism.

"Spotting," "breakthrough bleeding," and abnormally long periods are often caused by hypothyroidism. In the light of this knowledge, I feel that a physician who advocates removal of the uterus for excessive bleeding, without first trying thyroid therapy, is not practicing medicine properly.

Low body temperature (below 98 degrees when you wake in the morning) and slow pulse are the simplest indicators of hypothyroidism. Foolishly designed blood tests have caused many people to be taken off thyroid medication, in spite of their symptoms. For 40 years, time after time one blood test has displaced another, and always the one which is in use at the moment is "the correct" one. The oldest test, the BMR, is still the best, in spite of the possibility of a mistake if the test is given when the patient has an infection, but the temperature is also a reliable indicater (except that heat from the environment — an electric blanket or a hot room — can artificially raise temperature to normal.)

Cysteine, an amino acid which is abundant in muscle and liver, happens to block synthesis of the thyroid hormone. When we are starving or under stress, cortisone causes these protein-rich tissues to be consumed. If metabolism continued at a normal rate, stress or hunger would quickly destroy us. The cysteine which is released from muscle, though, inhibits the thyroid, so metabolism is slowed. Cortisone also inhibits the thyroid. Any stress, including heavy exercise, will cause this protective slowing of metabolism. The slow heart beat of runners is largely the result of this adaptive hypothyroidism. When we eat large amounts of muscle meats or liver the high concentration of cysteine suppresses the thyroid. Heart, eggs, skin (gelatin) and milk are more favorable to the thyroid. Other anti-thyroid foods are peanuts, soybeans, raw cabbage, radishes, broccoli, cauliflower, unsaturated oils (such as safflower, corn, cottonseed, and soy oils), and an excess of iodine. Amygdalin (nitrilosides, laetrile) which occurs in many nuts, seeds and grains, is also a thyroid inhibitor. Because iodate is used as a "dough conditioner" (to make bread water-heavy), the American eater often gets ten times more iodine than is recommended. Combined with unsaturated oils, as organic iodides, excess iodine can powerfully inhibit the thyroid. Manganese is needed to synthesize thyroxin, so a deficiency can interfere with thyroid function (coffee is a major source of manganese, and caffeine also stimulates the thyroid).

When a baby is being born, or when a person is experiencing other stress, such as an infection, or when a person gets old, the best known thyroid hormone, thyroxine, is not changed to the more highly active form, T3 (triiodothyronine) in the normal way. In these emergency conditions, reduced oxygen consumption is a useful adaptation, since the blood

is poorly oxygenated. Eating carbohydrate stimulates this conversion, so many additional calories of carbohydrate can be eaten without causing a weight gain (reviewed by C. Martin, 1978). Many people whose thyroid gland is suppressed by stress cannot respond to synthetic thyroxine, T4, since the same stress can block its conversion to T3. Natural thyroid, USP, is the most generally effective, but a non-prescription thyroid tablet is available at many health food stores.

Contrary to popular ideas about thyroid, the gland will resume its functioning after stopping the use of a supplement even if it has been suppressed, and sometimes taking thyroid will *increase* the gland's function to normal. Taking thyroid will sometimes help thin people gain weight, by improving protein metabolism, and it often helps people to sleep more soundly.

PROGESTERONE IN ORTHOMOLECULAR MEDICINE

In several ways, both progesterone and thyroid can be considered as primary regulatory hormones. Both of them regulate metabolism directly at the energetic and synthetic levels, both have a normalizing, anti-stress action on the pituitary, and each has a promoting action on the other. Both are blocked (or consumed) by stress, and promoted by light, and by good nutrition. Both oppose the effects of stress, and facilitate nutrition. Both *are* nutrients in cultures which eat the whole animal, including ovaries and thyroid.

Disregarding most of the information promoted by pharmaceutical companies, and the medical texts and journals which for thirty years have reflected the opinions of those companies (especially regarding the patented synthetic estrogens and glucocorticoids), we can trace a line of research and ideas on the sex hormones, from pioneers such as Loeb, Korenchevsky, and Selye, through a generation that continued to demonstrate the toxicity of estrogen, and the value of progesterone, including people like Lipschutz, Dalton and Soderwall. In my dissertation research under Soderwall, I had the opportunity to collect and assimilate data indicating an *increased* estrogen effect in aging animals, and recently, using radioimmunoassay for serum estrogen and progesterone, I have found a similar change in menopausal women, and Terry Parkening, who also studied under Soderwall, has used that technique to show that senescent infertility in mice is also associated with an increased ratio of estrogen to progesterone. My research showed that the probable mechanism by which estrogen excess causes infertility is through limiting the availability of oxygen. I showed that anti-estrogenic substances, such as progesterone or vitamine E, increased the oxygen tension in

the uterus. This anti-oxygen effect of estrogen suggests a convergence of reproductive aging research with Warburg's theory that damaged respiration is the primary defect in cancer, and also with Selye's observation that estrogen's effect resembles the first, shock phase of the stress reaction.

Early research had also shown that estrogen diminishes hepatic glycogen (Brunelli, 1935), while progesterone increases both blood sugar and liver glycogen (Gaunt, et al., 1939). It is well known that hypoxia damages the fetal brain, but probably less well known that hypoglycemia, either chronic or acute, can cause brain damage and retardation. Hypoxia, by lowering metabolic efficiency, will cause hypoglycemia. Estrogen causes hypoxia at every imaginable site, from lung, through vascular fibrin and extracellular collagen and edema, to intracellular metabolism. Estrogen is also synergic with insulin, lowering blood sugar and promoting fat synthesis. Estrogen, and another common respiratory toxin, excessive unsaturated fats, have both been demonstrated to cause the birth of small-brained, retarded animals. Recent studies imply that about half of the children identified as hyperkinetic have experienced gestational stress. The most urgent need for progesterone therapy, I think, is in preventing a continuing epidemic of brain damage. Beyond that, many studies have found that the use of natural progesterone increases the child's IQ, typically by around 35 points (though there are claims of consistent 200 IQ's), and produces personalities that are more "independent, individualistic, self-assured, self-sufficient, and sensitive" (J.M. Reinish, *The Female Patient*, April, 1978, p. 87). Protection against hypoglycemia is probably the main mechanism — diabetic mothers often have precocious children, if they aren't damaged by drugs and irrational diets. Ten to fifteen grams per pregnancy, at increasing dosage, stopping a few days before expected delivery, seems to be the optimum amount, when there is some sign of excessive estrogen or expected toxemia, such as continuing menstruation in the first 2 or 3 months of pregnancy. The AMA department of drugs has specifically excluded progesterone from the sex hormones which are "now contraindicated in early pregnancy" (*JAMA 239* (3) p.236).

Hypoglycemia (which can result from any respiratory defect) can produce malfunction of any tissue, but brain dysfunction and immune dysfunction are very common effects. Adamkiewics has shown that allergic reactions to a given substance will decrease from 100 percent to zero, when the blood glucose increases from, for example, 50 mg.% to 150 mg.% or more (also see Chernigovsky's book, *Interoceptors*). Progesterone (and thyroid) will help in most allergic diseases, including the autoimmune and "collagen diseases," because it helps to maintain blood sugar

(promoting respiration and improving use of fat, sparing glucose) and also because it stabilizes lysosomes. This polar opposition of estrogen and progesterone also involves the polar antagonism of cyclic AMP and cyclic GMP, and to some extent a related antagonism of various prostaglandins (it has been suggested that this involves different populations of lysosomes, but I suspect it has to do with the superoxide dismutase enzyme system, and its inhibition or activation, since one of my assays to determine the action of estrogen turns out to be an inverse indicator of S.O.D. activity). Although progesterone and cortisone both raise blood sugar and stabilize lysosomes, their effect on the brain is very different: in large doses, progesterone is sedative and anesthetic, while cortisone is stimulating, and cortisone causes changes in the brain which resemble aging. The dopamine-serotonin antagonism (e.g., in the control of prolactin secretion) can be modified by progesterone, thyroid, and other factors.

Pfeiffer has investigated the relationship of porphyria to certain forms of "schizophrenia," but I don't think he has mentioned that a good dose of glucose, or of an anti-estrogen hormone, such as testosterone or progesterone, will make the symptoms go away, just about as dramatically as Adamkiewics' glucose infusion will block inflammation or anaphylactic shock (incidentally, medical people just recently found that a large infusion of glucose was effective treatment in septic shock). Vitamin E, the old anti-estrogen, pro-fertility, pro-oxygen, anti-clot nutrient, is now recognized as a factor in the control of porphyrin synthesis. Adaptively, it is logical for a lack of oxygen (as at high altitudes) to stimulate synthesis of the porphyrin ring, to use in respiratory systems, as hemoglobin or catalase. Other schizophrenias that Pfeiffer investigated involve distrubances in copper, zinc, and histamine, so it is interesting to note that these are powerfully regulated by estrogen, progesterone, and thyroid. Oxidation of epinephrine to adrenochrome has been seen in the uterus under the influence of estrogen, with copper as catalyst.

Other investigators have noticed abnormalities of pigmentation associated with psychoses or other nerve-related disease. Parkinson's disease, for example, involves degeneration of melanin-rich nerves, and melanin has now been identified as a "progesterone receptor," at least in some lower animals.

Most of the known biochemistry of lithium happens to overlap the actions of progesterone, e.g., aldosterone antagonism. However, while lithium has an anti-thyroid action, progesterone supports secretion of thyroxine, and apparently inhibits the formation of reverse T3, that chemical blocks the action of thyroid hormone. I have seen several

women substitute progesterone for lithium, and several of these have then gone on to rely on nutrition and light.

While progesterone might seem to cure almost everything, we should be careful to use it only when the biochemical mechanism is fairly evident. A progesterone deficiency can be misdiagnosed, as (for example) epilepsy, Bright's disease, multiple sclerosis, or even estrogen deficiency (as in menopause). It can affect susceptibility to many conditions including herpes infections, dizziness, dysperception, varicose veins, mastitis, fibroma, and endometriosis. Cyclic edema, depression, and migraine are, in my experience, always stopped by progesterone. Sexual functions are often improved.

Progesterone is the precursor (following acetate and cholesterol) for all of the other steroid hormones, so it can be used in men. It (or its precursor, pregnenolone) has been used for prostatitis, arthritis, and infertility in men. Large amounts, though, would probably suppress LH, and lower testosterone synthesis, but a smaller amount (especially in old men) seems to increase sperm count and motility. In male and female athletes who become infertile, it would seem to be the appropriate therapy, generally in combination with thyroid.

Progesterone has been shown to be effective in many animal tumors, including pituitary tumors and other estrogen-induced tumors, and in human cervical and breast cancers. Since glucose metabolism is disturbed in cancer, it would seem reasonable to combine progesterone therapy with sufficient thyroid to maintain protein assimilation, and to provide a high protein diet to assure that the liver can excrete estrogen.

Even very intense emotional or perceptual symptoms typically disappear within 40 minutes when a dose of 300 mg. is given transdermally, dissolved in vitamin E or olive oil. Ovarian cysts, menopausal flushing, acne, sprains, and menstrual cramps can also be relieved with dramatic speed. In Addison's disease it can prevent some of the side effects of cortisone. Facial hair is often normalized in women. I have distributed about 25,000 doses of progesterone, and failure to use enough has been the most common problem. I always spend at least an hour with each person, learning about them and explaining relevant aspects of physiology and nutrition. I have each person read at least one book on the subject, such as the following:

K. Dalton, *Premenstrual Syndrome and Progesterone Therapy* (1978)

B. Barnes, *Hypothyroidism, the Unsuspected Disease*

R. Peat, *Mind and Tissue; Nutrition for Women; and my progesterone papers.*

DOSAGE OF PROGESTERONE

Since progesterone is not known to have any side effects except for alteration of the menstrual cycle and production of euphoria (until doses of several grams per day are reached, at which point its anesthetic property begins to appear), the basic procedure should be to use it in sufficient quantity to make the symptoms disappear, and to time its use so that menstrual cycles are not disrupted. This normally means using it only between ovulation and menstruation unless symptoms are sufficiently serious that a missed period is not important. The basic idea of giving enough to stop the symptoms can be refined by some information on a few of the factors that condition the need for progesterone.

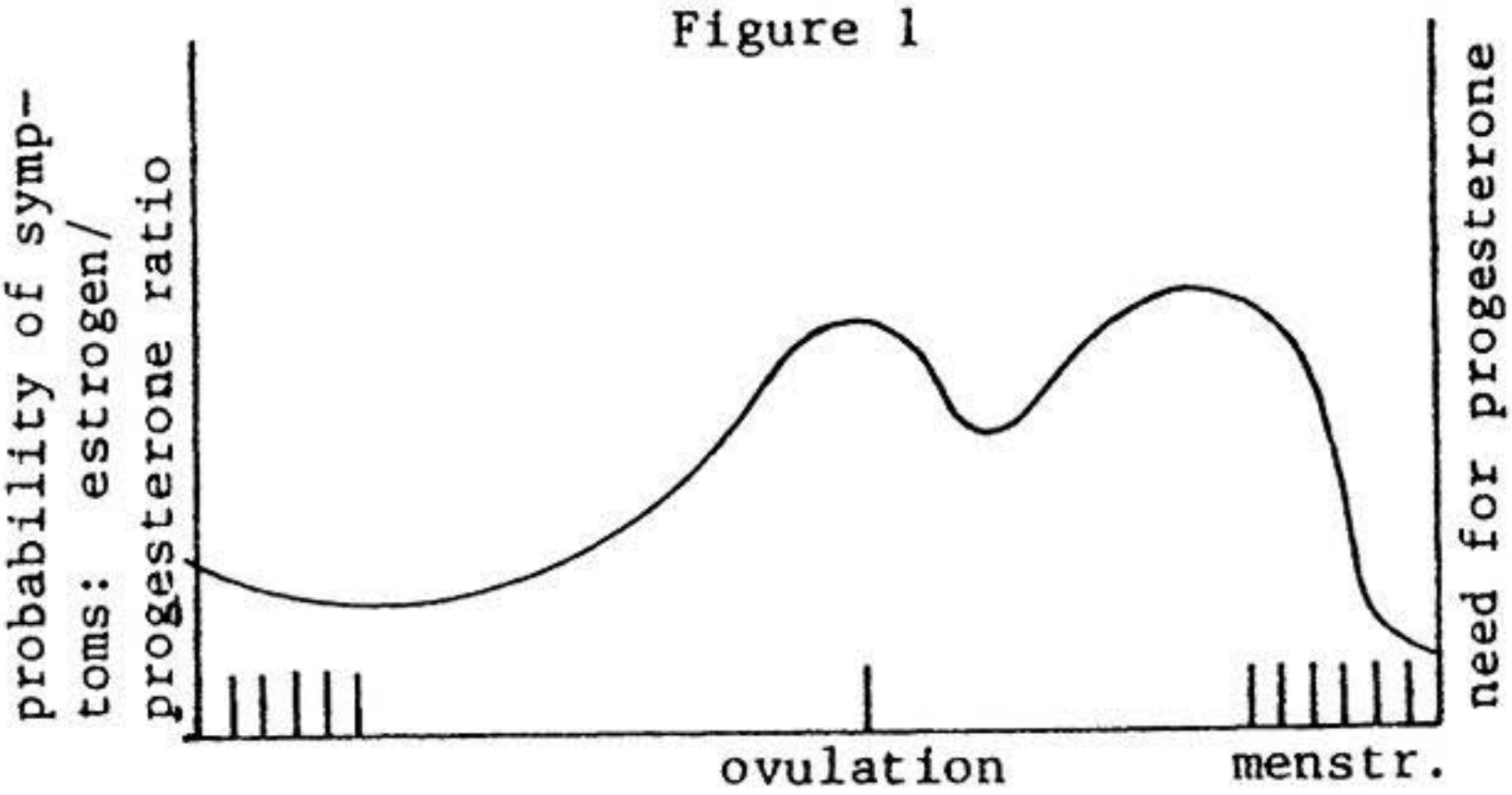
An excessive estrogen/progesterone ratio is more generally involved than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet, other steroids, thyroid, and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia (as reported in my dissertation, University of Oregon, 1972), and this is the result of changes induced by estrogen in alveolar diffusion, peripheral vascular changes, and intracellular oxygen wastage.

Hypoxia in turn produces edema (as can be observed in the cornea when it is deprived of oxygen, as by a contact lens) and hypoglycemia (e.g., **C.** Martin: diminished ATP acts like insulin), because glycolysis must increase greatly for even a small deficiency of oxygen. Elevated blood lactic acid is one sign of tissue hypoxia. Edema, hypoglycemia, and lactic acidemia can also be produced by other "respiratory" defects, including hypothyroidism, in which the tissue does not **use** enough oxygen – the skin will be bluer (in thin places, such as around the eyes) when hypoxia, rather than low oxygen **consumption**, is involved. Low thyroid is one cause of excess estrogen; when both are involved, the color of the skin is neither red nor blue, but relatively bloodless – white or yellow.

Symptoms in cycling women are most common around ovulation and in the premenstrual week, when

the estrogen/progesterone ratio is normally highest. The early twenties and the late thirties and menopause are the ages when the ratio is most often disturbed - and these are also the ages when thyroid disorders are commonest in women.

Figure 1



Besides a family tendency to have related symptoms, the individual who suffers from one aspect of the progesterone deficiency will tend to develop others at different times. With cyclic depressions or migraine headaches at age 22, there will possibly be breast disease and often there will be problems with pregnancy, and menopause may bring on a complete collapse.

Excess stress (by elevating estrogen and/or depleting progesterone, etc.) may bring on symptoms in someone who never had them. Spending a summer in Alaska, with an unusually long day, may relieve the symptoms of a chronic sufferer. Dark cloudy winters in England or the Pacific Northwest are powerful stressors, and cause lower progesterone in women and testosterone in men. Toxins, such as copper and lead, can produce similar symptoms. Porphyria and zinc deficiency are often caused by the hormone imbalance. A very common cause of an estrogen excess is a dietary protein deficiency - the liver simply cannot detoxify estrogen when it is undernourished (see Lipschutz references).

Figure 2

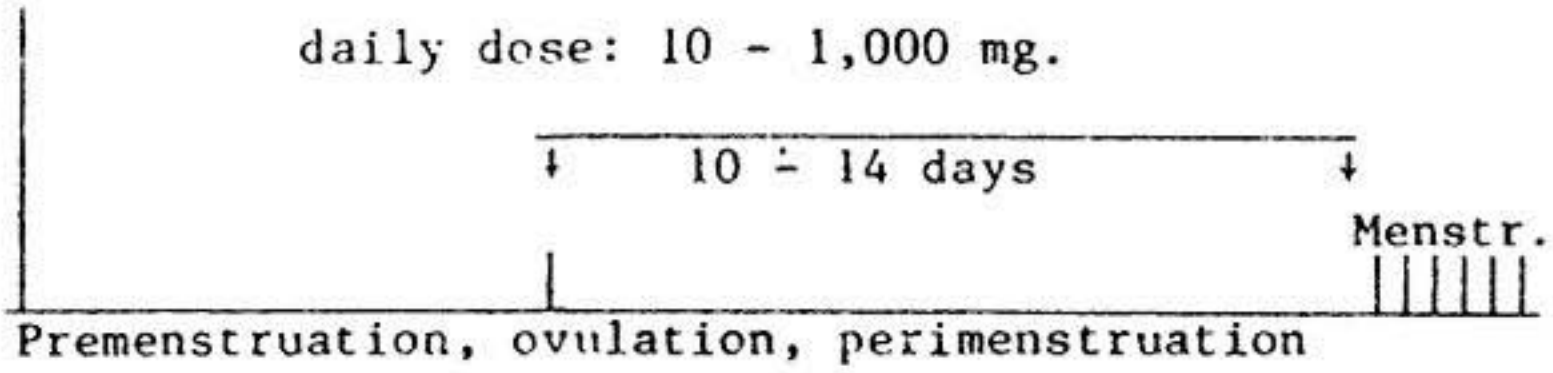


Figure 3

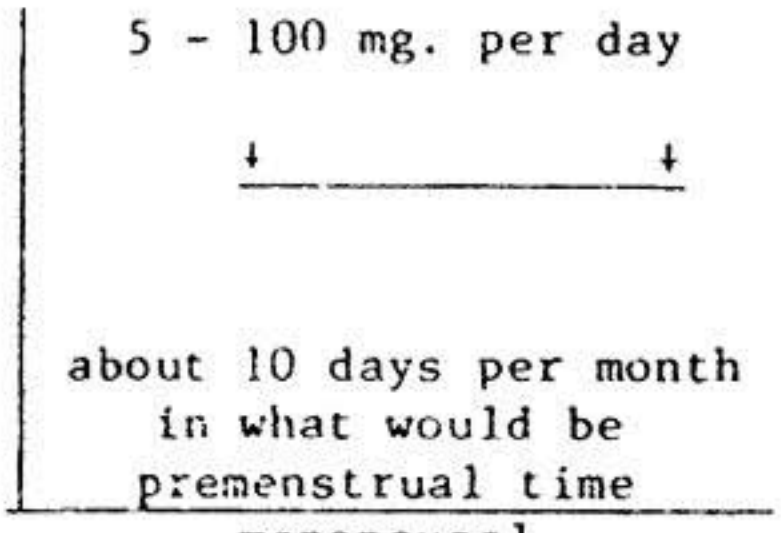
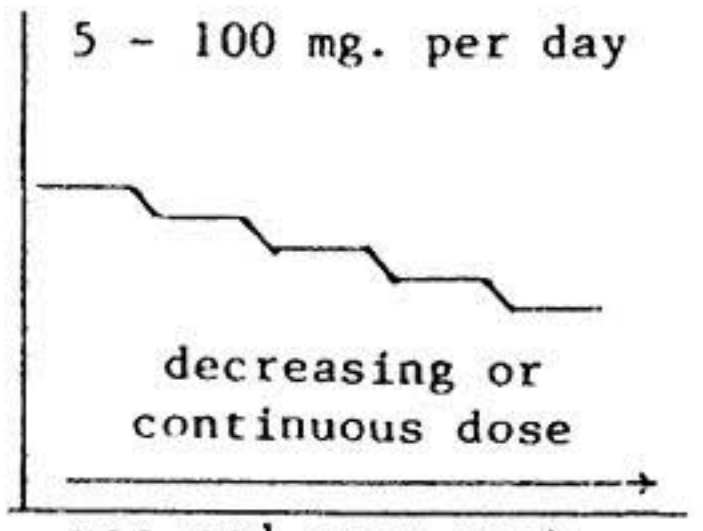


Figure 4



With a diet high in protein (e.g., 70-100 grams per day, including eggs) and vitamin A (liver once a week), I have found that the dose can be reduced each month. Using thyroid will usually reduce the amount of progesterone needed. Storage of progesterone apparently occurs in adipose tissue, so that one dose which is much bigger than needed will sometimes control the symptoms for several days.

Katharina Dalton, **Premenstrual Syndrome and Progesterone Therapy,** Year Book Medical Publishers, Inc., Chicago, 1977.

Alexander Lipschutz, **Steroid Hormones and Tumors,** Williams and Wilkens Company, Baltimore, 1950.

Raymond F. Peat, **Age Related Oxidative Changes In the Hamster Uterus,** University of Oregon thesis, Eugene, Oregon, 1972.

TRANSDERMAL PROGESTERONE FOR PREMENSTRUAL SYNDROME

For many years, Katharina Dalton[1] has studied the use of progesterone therapy for the premenstrual syndrome. A typical patient may require ten or more progesterone injections per month, more or less permanently. While this is feasible (at least in some countries) it is not comfortable or convenient, in some cases leads to serious reactions at the injection sites, and in the United States would be too expensive for general use. When the syndrome is disabling, even the burden of frequent and expensive injections is usually seen as a welcome alternative. However, a less expensive and more pleasant form of administration could make the therapy available to millions of women who are now disabled for one or more days each month. We are reporting here on what we believe to be a satisfactory alternative to the injection or implantation of progesterone, namely, a solution of progesterone and vegetable oil in a lotion or "cold cream" base for transdermal use.

After animal experiments revealed that progesterone in vegetable oil was absorbed effectively through the skin, in 1977 we began experiments with women who suffered from the premenstrual syndrome.

The effectiveness of the transdermal (absorption) route of administration varies with the individual, but compares favorably with injections in the amount assimilated. Thickness of skin or degree of circulation in the skin (these can be very abnormal in hypothyroidism, for example) and the amount of adipose tissue apparently make some difference in the rate of absorption and response. When a small daily dose (e.g., 5 or 10 mg.) is sufficient, this can be taken as about 250 mg. of a three percent cream rubbed into the throat, where it leaves no noticeable oiliness after a few minutes. For large doses, the appropriate amount can be applied to a larger area of skin after a hot bath, once or twice a day if necessary.

We have used transdermal progesterone therapy in two hundred women suffering from the full range of perimenstrual symptoms, including migraine, acne, depression, mastalgia, edema, and lethargy, and we found that nearly all of the women, applying the lotion themselves, are able to find the appropriate dosage for controlling their symptoms. Occasionally, thyroid therapy, weight reduction, or change in some aspect of life-style is

necessary for complete relief from symptoms. We have learned that it is necessary to be very explicit in describing the amounts that can be used, while leaving it up to the patient to find the dose which controls her symptoms, because some women have an exaggerated idea of the power of a "hormone". We have learned, when some women said the progesterone had no effect, that they were applying it as sparingly as they would a rare perfume, just touching it to their wrists.

Another problem we have encountered is that a few women have trouble understanding how, if their edema is caused by "hormones", a "hormone" could relieve the edema. We have usually solved such problems by applying one dose (sometimes using a twenty-five percent solution) in the office, and waiting thirty or forty minutes to make sure that it was large enough to take effect. Once having felt sudden relief from this "cold cream", it is easier for the patient to understand how it should be used.

Unfortunately, many of the solvents which hold progesterone stably in a concentrated solution are highly allergenic. Injectable progesterone in oil could be used transdermally except for this problem. Progesterone can be removed from an injectable water suspension, and dissolved in warm olive or almond oil for transdermal use in patients who react to other solvents.

[1]Katharina Dalton, **The Premenstrual Syndrome and Progesterone Therapy,** Year Book Medical Publishers, Inc., Chicago, 1977.

TOPICAL PROGESTERONE FOR ACNE

In a previous study which found topical progesterone ineffective as therapy for acne, the investigators used ethanol as a solvent[1]. When water is added to a solution of progesterone and ethanol, the progesterone crystalizes out of solution, because water and ethanol have a fairly high mutual solubility and progesterone is practically insoluble in a water-ethanol mixture. When the progesterone-alcohol solution is applied to the skin, the alcohol takes up moisture from the skin, which is sufficient to cause the progesterone to be left undissolved on the surface. We have tried other solvents, including olive oil and vitamin E, which are stable in the presence of moisture, and we have had consistently positive results in twelve cases of acne associated with the menstrual cycle (usually appearing or getting worse around ovulation or just before menstruation) and in one of two teenage boys with chronic acne.

Because of the poor solubility, or instability of solution, of progesterone in natural oils of variable composition, we advised the patients to warm the solution in a hot water bath before every application. The solutions varied from one to ten percent progesterone (i.e., one to ten grams per 100 ml. of oil). Patients applied the oil to the affected skin once or twice a day. The amount of progesterone applied ranged from about 25 mg. per day to about 250 mg. per day.

The patients (except for one of the teenage boys, who reported no effect), consistently reported that use of progesterone at the first sign of a pimple stopped the development at that stage, prevented the expected outbreak, and within a few days resulted in a relatively clear skin. The improvement ranges from complete freedom from pimples in half of the group, to "improved, but still visible blemishes" in three women. Some of the solvents (sandlewood oil, vitamin E) caused an "allergic" skin irritation in two women, but switching to olive oil eliminated those reactions.

[1]British Journal of Dermatology, Volume 99, Supplement 16, 9, July, 1978.

PROGESTERONE AND BODY TEMPERATURE

Women, more often than men, have "normal" body temperatures which are distinctly below normal, i.e., as low as 97 degrees, especially in the two weeks following menstruation. In men, giving progesterone doen't cause an increase in body temperature, though it usually does in women. Progesterone is at its lowest in the two weeks between menstruating and ovulating. The fact that progesterone isn't "thermogenic" in men suggests that its activity relates to estrogen, which is its "antagonist." It is known that thyroid hormone increases heat production, and that estrogen is in many ways antagonistic to thyroxin. Therefore, it is not surprising that progesterone, by blocking estrogen's blockage of the thyroid hormone, should promote the effect of thyroxin and raise the temperature. The metabolism is shifted toward oxidation of fat, with the result that sugar is spared for the brain and kidneys and, in pregnancy, for the fetus.

Nutrition which supports the adrenals, ovaries, thyroid and liver can raise the body temperature toward normal, while reducing premenstrual symptoms and dysmenorrhea. Usually, vitamins A, E, pantothenic acid, and C will raise the temperature; sometimes other B complex vitamins are needed, as well as minerals such as iodine, manganese, zinc, and magnesium.

During stress, the temperature is often above normal, even when there are symptoms of progesterone deficiency. I have noticed that this is usually associated with enlarged lymph glands, as if the adrenal cortex had become inactive. In this state, adrenalin (and ACTH) would continue to be secreted, possibly at high levels, since the cortex normally makes anti-stress hormones to take over some of the resistance-promoting effects of adrenaline, if the stress lasts more than an hour or so. Adrenaline shrinks blood vessels in the skin (preventing heat loss) while stimulating metabolism and so might account for this fever of stress.

Sometimes progesterone seems to be chronically deficient (leading to slight — though possibly prolonged — menstruation, or even amenorrhea), in women who exercise hard. Since progesterone can be converted into cortisone to handle stress, this could explain why well trained athletes (who need lots of cortisone) so often miss periods. It seems to be a simple over-consumption of progesterone, which is probably a reasonable biological adaptation, preventing pregnancy during times of stress.

BREAST SORENESS, CYSTIC OVARIES

Women with benign breast diseases are likely to have abnormally low progesterone levels, while their estrogen stays relatively high (Mauvais-Jarvis, *Annales d'Endocrinologie 37*, 309-310, 1976). This same imbalance may also play a role in breast cancer (Sherman and Korenman, *Cancer 33*, 1506, 1974). Since progesterone is a chemical precursor of cortisol, prolonged stress would tend to lower the availability of progesterone, unless the adrenal glands are very well nourished. Vitamin A is required for progesterone synthesis, as well as for proper maturation of cells in membranes and glandular tissue. Pantothenic acid, niacin and vitamin C are commonly limiting factors in synthesis of adrenal hormones. (Synthetic "progestins" are likely to *cause*, rather than to prevent, breast cancer, and should never be used; natural progesterone needn't be injected, as some doctors believe, since it can be absorbed through the skin.) Cystic ovaries are often associated with sore breasts. Animal experiments (Janes; Leatham) show that lack of thyroid hormone can cause cystic ovaries. (See article on estrogen-thyroxin antagonism.)

II. STRESS

BLOOD SUGAR: SOME TECHNICAL BACKGROUND

Sugar can be used to produce energy with or without oxygen, but oxidative metabolism is about 15 times more efficient than the non-oxidative "glycolytic" or fermentive metabolism; higher organisms depend on this high efficiency oxidation for maintaining integration and normal functioning. If there is a small interference with respiration, the organism can adapt by increasing the rate of glycolysis, but there must be enough sugar to meet the demand. A response to stimulation is the production of more energy, with a proportional increase of oxygen and sugar consumption by the stimulated tissue; this produces more carbon dioxide, which enlarges the blood vessels in the area, providing more sugar and oxygen. If the irritation becomes destructive, efficiency is lost: oxygen is either consumed wastefully, causing blueness of the tissue (assuming circulation continues; blueness can also indicate bad circulation), or is not consumed, causing redness of the tissue. As more sugar is consumed in compensation, lactic acid also enlarges the blood vessels.

If the inflamed or exhausted tissue is small, the lactic

acid can be consumed by other oxidizing tissues, sufficient sugar usually can be supplied, and repair occurs. But a large inflammation, or profound exhaustion, will lower the blood sugar systemically, and will deliver large amounts of lactic acid to the liver. The liver synthesizes glucose from the lactic acid, but at the expense of about 6 times more energy than is obtained from the inefficient metabolism — so that organismically, that tissue becomes 90 times less efficient than its original state. Besides this, an idle destruction of energy molecules (ATP or creatine phosphate) will increase the wastefulness even more.

When the organism detects the inflammation or other stress (possibly by sensing changes in blood sugar, lactic acid, or carbon dioxide, or all of them) its adrenal glands will secrete anti-stress hormones, including adrenalin and cortisone (assuming these glands are not exhausted or starved). Both adrenalin and cortisone can raise blood sugar to meet the increased need. Cortisone stimulates the conversion of protein to sugar, and since there are no "stored proteins" (other than small amounts circulating in the blood) this means that cortisone starts the conversion of the organism into fuel for the problem area. In acute emergencies, the lymphoid tissues will shrink first, which is all right, since they can be restored after the animal recovers, and their function — immunity — is partly a matter of a longer time scale, days to weeks. But if these tissues are chronically depleted by stress or malnutrition, infection is more likely to be fatal, as in old age or in poor populations. (The connection between infection, stress and sugar was illustrated recently by the discovery that infusing large amounts of glucose can relieve septic shock.)

Carbonated water can provide enough carbon dioxide (sometimes) to improve the delivery of blood (and glucose) to the brain. Low thyroid leads to low production of carbon dioxide and to wastage of glucose.

Various nutritional, hormonal, or toxic states interfere with respiration in different ways: for example, vitamin E deficiency, estrogen excess, toxic thyroid, and DNP (the formerly popular cancer-causing reducing drug) cause oxygen to be consumed without producing the normal amount of useful energy. Vitamin B2 or copper deficiency can prevent consumption of oxygen. Cancer (contrary to a tenacious establishment doctrine) involves a respiratory defect, and causes a tendency toward hypoglycemia which is often compensated by the conversion of protein to sugar, leading to the terminal wasting state (cachexia). (See Shapot and Blinov, *Cancer Research 34*, 1827-32, 1974.)

Vasodilation, edema, local heat and acidity are early responses to an irritant or energy defect; later, increased

collagen production and capillary proliferation occur. Tumefaction and tissue death can result if the organism's resources aren't adequate.

Sugar wastage, leading to lactic acid production, can result from a vitamin B2 deficiency, and lactic acid appears to stimulate vascularization (Imre, 1964; *Exp. Eye Res. 25*, Supplement, 1977, P. 284). This would relate to the development of blood supply to cancers, and also to the blood-shot eyes and red noses and cheeks of alcoholics and others who are deficient in vitamin B2.

In general, stress should be met first by correcting the defect, which may be environmental or nutritional. Increased nutritional needs usually include protein and fat; acute hypoglycemia may require a large amount of sugar, and this suggests that the adrenals may be depleted, in which case pantothenic acid, vitamin C, vitamin A, magnesium and potassium should be provided in addition to other nutrients.

Sometimes, sugar has to be eliminated permanently to control hypoglycemia. Some people have to eat a snack (e.g., a small slice of cheese) every hour, but this can often be overcome if the liver is able to recuperate.

Pantothenic acid is needed by the liver to destroy insulin (insulinase), so hyperinsulinism, causing hypoglycemia, can sometimes be remedied with this nutrient.

STRESS AND SPECIAL NUTRITIONAL REQUIREMENTS

According to Hans Selye, activation or injury of tissue is the beginning of stress. The more cells involved, the greater is the stress. An injury to a leg connected only by blood vessels produces a stress reaction in the animal, so the signal of stress can be transmitted in the blood, though the nerves are normally also involved. Adenine nucleotides have been suspected as a cause of shock (because they are vasodilators, as are many other products of stress, including phosphate), but other possibilities are histamine, various polyamines, and low blood sugar.

Selye divides stress into three phases: alarm, resistance (or adaptation), and exhaustion. Three tissues are usually the first to show effects: thymolymphatic tissue shrinks, gastrointestinal tissue becomes inflamed and bleeds, and the adrenal cortex becomes enlarged.

Selye classifies steroids into anti- and pro-inflammatory. Inflammation is a relatively non-specific, and hopefully local, reaction, serving to isolate the problem if it is a toxin or infection. Cortisol is a typical anti-inflammatory hormone; DOC (deoxycorticosterone) is considered by Selye to be a natural pro-inflammatory steroid, but other endocrinologists point out that it is normally present only in very small

amounts, as a precursor of aldosterone (which helps retain sodium in stress — sodium probably helps activate the glycolytic pathway, speeding the use of sugar). Some of Selye's stress experiments involved giving a large dose of sodium, presumably increasing the amount of DOC in the tissues, and intensifying stress symptoms.

Injury and exertion have in common the need for more fuel. I think the blood sugar level is therefore useful at least for understanding stress, even if other substances are involved in the "signalling" or coordinating process. From my own experience, I am inclined to believe that blood sugar is an important integrating factor, and that the organism can probably sense small or rapid fluctuations that would be very hard to detect by the usual laboratory procedures. For example, males in particular are known to secrete adrenaline under the stress of having blood drawn, and this tends to raise the concentration of blood sugar. Even when extremely large and prolonged variations in blood sugar are found, the concept of "normal range" allows most physicians to dismiss them as being insignificant — even when the patient develops classical symptoms of hypoglycemia: if the patient faints or has convulsions when his blood sugar falls 50 mg.%, the physician is likely to note the "psychosomatic reaction" or the "coincidental epilepsy," since a "normal variation" in blood sugar concentration supposedly couldn't be responsible. More physicians are now recognizing that the rate of fall can be as important as the absolute level.

Hans Selye sometimes used an injected metal, such as iron salts, to experimentally sensitize animals to stress, making it easier to produce arthritis. He found that vitamin E could offset this effect of iron.

SUGAR AND THE PANCREAS

Ordinary refined cane or beet sugar is sucrose, a "double sugar" or disaccharide. (Some of this chemical terminology is useful for understanding food lables.) The two units making up sucrose are glucose and fructose. These are monosaccharides, and since they contain six carbon atoms, they can also be called hexoses. Glucose is classed as an "aldose" because it contains an aldehyde group: by just shifting the position of two hydrogen atoms onto this aldehyde group, glucose turns into fructose (a keto sugar or "ketose").

Carbohydrates are usually split into monosaccharides before being absorbed. They are carried to the liver, where glucose can be used to replenish the storage form of carbohydrate, glycogen. If there is more glucose than the liver can store, it reaches the pancreas where it stimulates

the release of insulin, which disposes of the sugar by stimulating synthesis of fat and glycogen. The insulin is only slowly degraded, so it will go on lowering blood sugar if sugar isn't being absorbed continuously from the gut. If blood sugar gets too low, an alarm reaction will produce adrenalin to restore blood sugar, with the result that the person may feel anxious.

Insulin should be about 30% destroyed by the liver each time the blood circulates to the liver, but a pantothenic acid deficiency will prevent this regulation. Low thyroid also interferes with liver function limiting the storage and release of glycogen.

Fructose doesn't stimulate the pancreas as glucose does. It is gradually converted into glucose. In people with high blood lipids, however, it is utilized by liver and fat tissues several times faster than it is in normal people: it is as if the cellular "doors" were already open in these people, maybe as a result of high insulin levels, and the cells accept fructose more rapidly than normal. This doesn't imply that fructose is to be avoided as rigidly as is glucose, since I don't think there is any evidence that it initiates any problem. Grapes are rich in glucose; other fruits have varying quantities of fructose: honey contains some fructose. Jerusalem artichokes that have been kept in storage are a very good source of fructose. Onions are another source. I suspect that even glucose wouldn't be so hard on the body if it were always taken with potassium and other nutrients involved in its metabolism.

Potassium is necessary for utilization of sugar, and should probably always be tried as a supplement in the diabetic diet, especially since fruits, an important source of potassium, may be avoided because of their sugar. Some B vitamins (B1 and B2 and probably niacin) are said to have similar effects on the utilization of sugar. Some forms of diabetes involve normal or high levels of insulin, others, a lack of insulin; both have been found to respond to nutrition, but especially the high insulin form. The pancreas can be damaged by prolonged malnutrition, so that the inability to produce insulin may be permanent. Magnesium and vitamin B6 deficiencies are known to be involved in damage to the pancreas. Insulin itself is only part of the "insulin-like" system (*Adv in Metabol Disorders 7*, p.26, 1974); proper treatment requires a proper study of all factors. I know of children who have been put immediately on insulin, for life, after one urine test showed glucose, even though the test followed a stressful infection. Stress can cause sugar to appear in the urine, as can many other conditions, and this does not call for insulin treatment.

EMOTIONAL PROBLEMS

Just before menstruation begins, and just after giving birth, the level of estrogen in the body can be high, and out of proportion to other hormones. Tension, anxiety, depression, being too easily upset emotionally, and even having hallucinations can result from this hormone imbalance. Excess estrogen causes the body to accumulate copper, and copper poisoning itself (often caused by water that is contaminated, for example by plumbing, a hot water heater, or utensils) is known to cause symptoms of schizophrenia. Menopause is another time of frequent emotional upsets, for many women. A type of psychosis sometimes occurs at menopause. Since it is easier to test for excess copper than for excess estrogen, it might be worthwhile to have this test done when there are emotional problems during menopause, around menstruation, or in the first few weeks after giving birth. Tension resulting from too much copper or estrogen can be relieved nutritionally. Usually a zinc supplement is necessary — about 20 mg. a day; about 30 mg. of vitamin B6 has been recommended for this problem, but the amount varies with the individual. The other B vitamins, and vitamins E and A should also be used. Sometimes as much as 500 mg. of niacin can be required to stop a "hysterical" feeling. The mildly sedative action of magnesium can also have a dramatic effect. One half to one gram of magnesium is enough if it is taken in a highly soluble (and assimilable) form such as magnesium chloride. Since low blood sugar is often a factor in anxiety or depression, adequate protein and calories must be eaten regularly. Biotin (1-2 mg.) can stop some depressions. Fruit is very useful in maintaining blood sugar since it provides sugar with potassium which helps to avoid an insulin reaction.

PEOPLE DIAGNOSED AS "PSYCHOTIC"

Women are increasingly being diagnosed as "manic-depressive," though this used to be thought of as mainly a man's disease. I think the new popularity of lithium "therapy" has contributed to this diagnostic trend. Even if the problem is what had previously been described as "premenstrual depression," lithium therapy does work, though some patients complain of tremor, dullness, and clumsiness.

Several of the known biochemical effects of lithium are similar to those of progesterone, including antagonism to aldosterone, modification of serotonin metabolism, elevation of nerve thresholds, and facilitated disposition of ammonia.

(Other psycho-active chemicals which have some overlap with progesterone are DOPA, bromocryptine, and physostigmine.)

One type of "schizophrenia," and the very common symptom of "agorophobia" or reclusiveness, are associated with high levels of porphyrins and pyrroles. Fasting, liver damage, and increased estrogen levels can raise the concentrations of certain of these substances; they seem to promote urinary loss of zinc and vitamin B6. Estrogen promotes copper (and iron, and calcium) retention, and copper tends to displace zinc. The high levels of copper, iron and lead which are found in many people with mental problems may be secondary to a hormone disturbance. Thyroid gland or progesterone, or both, can produce a complete disappearance of mental symptoms when those symptoms result from any biochemical imbalance that can be rectified hormonally, because these two substances have very generalized regulatory functions. I feel that any "diagnosis" (naming in Latin) of a "functional mental disturbance" is at best irrelevant, and may be very destructive. People with diagnoses of "schizophrenia," "epilepsy," "manic-depressive psychosis," "Parkinsonism," "myasthenia gravis," "involutional psychosis," "neuritis," "sclerosis," etc., have reported that they felt normal or improved after taking progesterone, often within 40 minutes. Magnesium, as epsom salts or magnesium chloride or carbonate, can relieve some cases or irritability and tension, even when something else, such as hypothyroidism, is the basic cause.

Many symptoms have been blamed on cerebral edema, which might result from too much estrogen. However, the speed with which some symptoms disappear suggest other possible explanations. Just as veins in the forehead shrink immediately if a *large* amount of sugar is taken for a migraine, I have seen veins (back of hand) disappear with progesterone treatment, just when a suicidal depression is lifting. This suggests that there may be a "migraine" condition in the blood vessels of the limbic system of the brain, but there are also very rapid shifts in brain chemistry.

Light and smell are known to affect hormone production. A musky material (Le Magnen's "exaltolide," probably includes androstenol) is probably a social regulator of hormones — perfume containing musk might affect the woman who wears it. Bright lights for 18 hours per day can correct some hormone-mood problems.

Canker sores, herpes infections, and bleeding gums, if associated with mental symptoms, suggest a thyroid and/or progesterone deficiency.

CANCER PRODUCES STRESS

Cancer overstimulates the anti-stress adrenocortical hormones, and usually produces extreme wasting from mobilization of fat and protein; blood sugar and glycogen storage are disturbed. During or after cancer treatment the "hypoglycemia" diet seems desirable: frequent small feedings, liver (or similar nutrients), magnesium, potassium. Vitamins A, E, C, and pantothenic acid are particularly important in stress, but all nutrients are necessary.

In an article on inflammation, the Encyclopedia Britannica makes this comment which is extremely interesting in connection with the fact that cancer involves a failure of the immune reaction:

> Severe starvation or...deficiency of protein may restrict antibody formation. Hormones of the adrenal cortex in sufficient amounts depress formation of certain types of antibody. The adrenal cortex secretions are capable of altering the inflammatory reaction in several ways: excessive amounts of the hydrocortisone type of secretion reduce the quantity of exudate formed and the amount of fibrous tissue and capillary proliferation.

About 1950, prisoners were experimentally injected with cancer cells; those who already had cancer developed tumors where cells were injected; healthy patients apparently never developed cancer, though a reasonable follow-up wasn't done. Cortisone treatment is known to speed growth and spreading of injected cancer cells. Cancer patients are typically unable to even produce a normal inflammation, as if they are powerfully dosed with the anti-stress cortisone-type hormones. The failure of the immune system, which can normally wipe out cancer cells as they develop, seems to be an essential feature of cancer, and as quoted above, adrenocortical hormones can suppress antibody formation; the conversion of body protein to sugar (an effect of these hormones) causes shrinking of the thymus gland, which is essential for healthy immune reactions. Although there may be other things involved in the immune suppression, part of it appears to be this drain on the body's protein, which can be alleviated nutritionally. Dr. W. D. Kelly (*One answer to cancer*) describes an interesting test for cancer based on this problem in protein metabolism. A drop of blood squeezed from a puncture in the finger should stand up in a spherical drop, but when a person is developing cancer it spreads instead of rounding up. (See the section on

edema)

Stress apparently increases a person's need for all nutrients including calories and protein. The vitamins most commonly used for resisting stress are A, C, E, and pantothenic acid. The minerals magnesium, calcium, potassium and zinc can help in the first stages of stress, and sodium supplements may be needed in the last extreme stage of stress when the adrenals have been exhausted.

ARTHRITIS AND STRESS

Dr. E. C. Barton-Wright and Dr. W. A. Elliot have found pantothenic acid (at least 25 to 50 milligrams per day) useful in arthritis. Arthritis is commonly a result of stress, stress increases the need for that vitamin and also for other nutrients including vitamins A and C. Arthritis often follows surgery. Sometimes surgery can bring on chronic allergic problems (hay fever, gas, fatigue, etc.) but it can also apparently weaken the immune system so badly that old allergies disappear after an operation.

Stress inhibits the thyroid, and can lower progesterone (and/or testosterone) while raising estrogen. Recent work by Siiteri and his group shows a hormonal involvement in various "autoimmune" diseases. Females are much more susceptible to these sicknesses than are males. Systemic lupus erythematosis and rheumatoid arthritis are common.

Vitamin A offsets a protein deficiency, and a protein deficiency can damage immunity.

Any activity, if planned and completed according to plan without interruption, can reduce stress. Enforced inactivity, and inability to achieve what was intended, are powerful stressors. The adrenal hormones and mineral metabolism are disturbed in stress, whether the cause is a disorganized style of life, or the injury of surgery. The diet should include about 90 grams of protein (in frequent feedings), eggs as a source of sulfur (needed to synthesize joint lubricants, for example), and should keep the ratio of magnesium to calcium high (as with vegetables, bran, fruit), and the phosphate intake low (this would include using green leaves in place of some meat, as well as using cheese). Vitamins C, E, and pantothenic acid are needed in especially large amount in stress. Vitamins A and B2 are also essential for production of the anti-stress hormones. Inositol is known to protect biological materials from many kinds of damage, and might have this effect in arthritis, but I don't know of any research in this particular application.

Iron salts, and other heavy metals, have been shown by

Hans Selye to produce arthritis, possibly by their ability to destroy vitamins E and C.

Copper is a "specific" oxidant for vitamin C. It is associated with many inflammatory diseases, and should probably be better investigated in "degenerative" diseases, including arthritis and glaucoma.

Pantothenic acid in very large doses was recently found to protect against stress even when an animal's adrenals were removed. Since the nutrient is needed to destroy insulin, I think part of its anti-stress effect comes from minimizing hypoglycemia, and so reducing the amount of cortisone needed.

On the cellular level, stress lowers the energy charge. Systemically, stress inhibits oxidative metabolism. Both of these observations indicate that the "basic" anti-stress hormone would be thyroid. Hypothyroidism often involves arthritis — sometimes the tiny bones of the ear which transmit sound are affected. Ringing of the ears and deafness for high sounds are common in hypothyroidism.

M. Kirchgassner and H.L. Mueller, "The effect of varying the protein diet on the trace elements content of early-weaned piglets." *Landwirtsch Forsch 27* (314), p. 358-364, 1974: "copper/dry body matter clearly fell when the protein supply was increased." (And zinc rose.)

CORTISONE

About 25 years ago cortisone was found to increase the metastic spread of cancer. Since it raises blood sugar by dissolving protein from the tissues, the immune system and muscles are damaged. When the muscle mass is diminished, loss of fat becomes more difficult. Vitamin A can apparently help offset immunosuppression by cortisone. Use of cortisone can result in puffiness and water retention. It is a way of exaggerating the body's normal hormone response to stress, and may be justified if the adrenal glands are damaged. Pantothenic acid and vitamins C and A can help restore the glands' natural activity.

Vitamin B2 deficiency is also known to affect the adrenal glands, and has been suspected of contributing to the development of Addison's disease.

Vitamin A offsets a protein deficiency, and a protein deficiency can damage immunity.

Cortisone causes the liver to produce estrogen.

III. AGING

AGING

Some people who are supposed to be "experts" quite crazily claim that what you eat has nothing to do with how fast you age. Experiments with animals, observations of other cultures, and even some experiments with humans have shown clearly that nutrition can have a profound effect on the body changes which are called aging. In the three regions where a very high proportion of the population lives to be more that 100, the average daily calorie intake is only about 1500, which is considered "inadequate" by most nutritionists. Animals which are kept on a low calorie diet live much longer than those that are fed more, so we can assume that the low calorie diet contributes to the long life of those three groups. However, other similarities have been found in the diets in those three regions. Their food is fresh, they use a lot of animal fat (e.g., milk and cheese), they regularly eat greens, and some of them tend to drink quite a bit of alcohol. though in unrefined forms such as wine.

All of the essential nutrients are needed constantly to prevent deterioration of the body. At different times, nutrients such as vitamin C, pantothenic acid, or vitamin E, have been identified as methods to prevent premature aging. In our culture, many people do have severe deficiencies of those nutrients. but any dietary deficiency can cause degenerative changes. I have experimentally reversed a variety of degenerative changes with special nutrition, but the problem always exists within a particular person's physiology, and can't necessarily be solved by a standardized diet. You have to learn to know what your body needs at a particular time. This will be made easier if your basic diet is roughly like that described above — moderately low calorie intake, fairly high protein intake, with high quality proteins such as eggs, milk, and leaves, and with fresh fruit or vegetables every day.

Study of many different species, including humans, shows that aging is slower in individuals that have a larger brain in relation to body size. Brain size is strongly influenced both by prenatal nutrition and by nutrition in early childhood. The first year and a half is extremely important for the development of intelligence, since brain cells are still becoming more numerous up to that age, but growth and development of the brain can still be stunted by poor nutrition later. Progesterone is an important factor in brain development: estrogen inhibits brain development. Unsaturated fats also inhibit brain development if used in excess, and recent studies show that they also increase visible aging of the skin.

MENOPAUSAL FLUSHING

I have talked to several women in their 20s who complained of sensations of heat around their heads, night sweats, sudden flushing, and other symptoms that are associated with the menopause. Katharina Dalton has found that premenstrual symptoms, which result from a relative estrogen surplus and a progesterone deficiency, often continue during the menopause. Siiteri and his group have discovered that one of the steroids (androstenedione, usually associated with the male hormones) is converted to a form of estrogen at an increasing rate as a person gets older, at all ages they studied, from 20 to 80, in both men and women. Strickler found that only 10% of his patients with menopausal symptoms such as flushing, could feel and benefit from estrogen when it was alternated with a placebo. These studies, and a few dozen others, have convinced me that the symptoms of menopause result mainly from a progesterone deficiency, relative to the estrogens. The 10% who really feel better from estrogen *possibly* have an estrogen deficiency, but this has not been determined, and several other things could account for the "lift" they feel — for example, a *healthy* thyroid gland will respond to elevated estrogen with an increased output of thyroxin, which at least would make the person feel different, and might raise blood sugar, increase alertness, etc.

In 1979 menopausal flushing was found to be associated with an elevation of the pituitary hormone, LH. A lack of progesterone is known to cause a rise in LH.

Digitalis and progesterone have very similar effects on the heart (Szent-Gyorgyi, *Muscle Contraction*). Digitalis is able to raise blood pressure and increase urine production, apparently by increasing the tone of the arterioles (Abram, 1910). If progesterone's effect on muscle includes such an effect on arterioles, then the "puzzle" of menopausal — and premenopausal — flushing is no puzzle, but is merely one symptom of a progesterone deficiency relative to estrogen. Progesterone does have a diuretic effect, but this has been attributed to an antagonism to aldosterone, rather than to an effect on arterioles.

Besides the nutrients needed to regulate the estrogen level (protein and B vitamins) and nutrients needed by the thyroid (e.g., iodine, manganese, and cobalt), special attention should be given to the anti-stress vitamins which are involved in progesterone synthesis (vitamin A, pantothenic acid, vitamin C, vitamin E) and to the nutrients that are known to be "wasted" by excess estrogen: folic acid, zinc, and vitamin B6, particularly. Vitamin B6 is needed to synthesize materials that regulate blood vessel tone and that act as

brain modulators, governing sleep, emotions, alertness, etc. Memory of dreams is said to be promoted by adequate B6 (Pfeiffer, 1975). White marks on the fingernails, especially of the right hand, are suggestive of a zinc deficiency. Brittle fingernails are likely to result from too much estrogen, or inhibited thyroid function; vitamin A and eggs are useful, but calcium and gelatin are not. Magnesium carbonate is very useful for stabilizing nerves and muscles while raising the energy level: one gram a day of magnesium is a reasonable amount, but many tablets now contain only 15 to 50 mgs.

Dalton, K., *The Premenstrual Syndrome*, C. Thomas. Springfield, Ill., & London, 1964.

Hemsell, et al., Plasma precursors of estrogen. II. Correlation of the extent and conversion of plasma androstenedione to estrone with age, *J. Clin. Endocrinol. Metab. 38*, p. 476, 1974.

Grodin, et al., Source of estrogen production in postmenopausal women, *J. Clin. Endocrinol Metab 36*. p. 207, 1973.

Strickler, *Contemporary Ob/Gyn*, August, 1976.

Mulley and Mitchell, *Lancet*, June 26, 1976, p. 1397, "Is estrogen therapy justified in menopausal flushing?"

C.C. Pfeiffer, *Mental and Elemental Nutrients*, Keats Publ. Co., 1975.

SIMILARITY OF MENOPAUSE AND CUSHING'S SYNDROME

Excess estrogen is known to cause hypertrophy of the adrenal cortex. Since estrogen stimulates insulin release and lowers blood sugar, the hypertrophy may be to compensate by raising blood sugar.

The distribution of fat is similar in aging and in Cushing's syndrome. Vitamin E is known to shift enzyme activities in a way that would offset this distribution, and this might occur in cases caused by hormone disturbances other than mere aging.

The fall of spermine which occurs in senility, in estrogen excess, and in hypoglycemia should also be investigated in Cushing's syndrome.

The changes in endometrium, and the "castrate" type of vaginal epithelium are similar in both states. (Is the influence of contraceptive pills on vaginal epithelium what causes pain in intercourse?)

Osteoporosis and diabetes are frequently part of Cushing's syndrome, and are also more common after the menopause. Cortisone therapy (even when used on the skin) can cause mineral loss — recently an 8 year old girl who had

stopped growing was found to have osteoporosis resulting from use of a cortisone ointment. Thyroxine elevates magnesium levels in the tissue and is known to promote bone regeneration and mineralization. Estrogen's antagonism to thyroxin is so general that we could suspect that it would also inhibit healthy mineralization. Estrogen has long been used during and after the menopause for its supposed ability to prevent osteoporosis, but this is now known to be incorrect: any beneficial effect it has on osteoporosis is only temporary (C. Martin, *Textbook of Endocrine Physiology*, 1976).

In animal experiments, it has been found that cortisone can produce diabetes, apparently by damaging the pancreas, and it has been supected that chronic stress (which can be brought on by low blood sugar) can be a factor in producing diabetes.

Aging, stress, menopause, Cushing's syndrome, and the premenstrual syndrome all overlap so much that each state can probably give us some insight into the others. An elevated estrogen/progesterone ratio is likely to be a common feature.

CHOLESTEROL

A recent newspaper article about a former Oregon politician says "He was in excellent physical condition." "So for all these years, he hasn't smoked, he's kept his weight down to his normal 165 pounds. He has cut down on eating fatty foods and has watched his diet carefully." "I was in good shape," he said in his hospital room after being treated for the nearly fatal heart attack he had while jogging. I quote this because it shows how taking certain stylish "precautions" can give a person a false sense of security. Since a healthy liver will produce cholesterol to make up for what is lacking in the diet, avoiding high cholesterol foods won't necessarily lower blood cholesterol. In an article called "Fat has less cholesterol than lean," Raymond Reiser of Texas A & M University points out that 100 grams of a chicken drumstick has 91 mg. of cholesterol, while pork has only about 60 mg. per 100 grams. "On the calorie basis," he says, the cholesterol content of lean cuts "is about 4 to 6.6 times as high" as that of fat.

Vitamin C is now known to lower blood cholesterol. Eggs are rich in cholesterol, but they also contain lecithin, which appears to make the cholesterol useful, or at least less harmful. Niacin and vitamin E also help to regulate cholesterol. High insulin levels, caused by eating sugar, seem to be important in allowing cholesterol to damage the blood vessels. Cholesterol is used in the production of many hormones, including sex and anti-stress hormones.

High cholesterol usually indicates low thyroid function. When thyroid is low, cholesterol isn't converted efficiently into progesterone. The real cause of heart attacks seems to be hypothyroidism and its effects, including loss of magnesium. Stressful exercise can aggravate hypothyroidism.

AGING SKIN

Although estrogen is known to advance the aging of collagen in all tissues that have been studied, including skin, it has been promoted as a "youth drug." The beef industry uses it because it makes cows swell up with fat and water, to increase profits: it is no longer legal to soak meat — except ham — in water before weighing it for sale. Women, like cows, will puff up with water and fat under the influence of estrogen, and wrinkles will naturally be smoothed out, but the skin itself is actually losing its elasticity faster when estrogen is used. Testosterone and progesterone both have direct anti-estrogen activity. Testosterone lotion was tested on one armpit of an old woman. Her tissue had atrophied so that there was no hair, the sweat glands didn't function, and the skin was thin and wrinkled. After several weeks of daily use of the lotion, hair and sweat glands had returned to normal, and the skin was thicker, firmer, and smoother (photographs were published). Her other armpit remained as before. Progesterone has been found to reverse the chemical changes which occur in collagen with aging. In pregnancy, progesterone is probably responsible for the formation of relaxin, a hormone which makes the fibrous tissues become very stretchy, so the birth canal can open without damage. Some women notice that joints become very limber for a few days every month, suggesting that relaxin can be formed even when the woman is not pregnant.

Some of the changes of aging probably relate to "auto-immune" reactions, in which the body attacks itself: both testosterone and progesterone normalize the immune system, suppressing auto-immune problems. There are several dietary practices which will promote the formation of progesterone, but the most effective is to use liver once a week, to use eggs daily, and to avoid foods which inhibit the thyroid, such as raw cabbage and broccoli. Butter contains some progesterone. Young women might grow moustaches if they used testosterone cream on their skin very often (one day a month, at ovulation, women normally produce considerable testosterone) but natural progesterone lotion could be used safely for its effect on collagen. Progesterone has also been used to eliminate excess facial hair (photographs of this effect of progestins have been published in the *J. of Steroid Biochemistry*). Synthetic hormones are certain

to have side effects.

ESTROGEN AND OSTEOPOROSIS, ETC.

Estrogen has been promoted (on grounds that are at best dubious) as a therapy for menopause, for aging skin, for heart disease, for cancer, for premenstrual syndrome, for endometriosis, for preventing miscarriages, for nervousness and depression, for abnormal bleeding, and for osteoporosis. From Sept. 21, 1977, drug companies are required to give doctors and druggists brochures with estrogen, warning of the risk of cancer, and advising that estrogen not be given for nervousness, depression, or for "restoring youthfulness" during menopause, because it is ineffective for those purposes (UPI, July 20-21, 1977). However, they failed to mention studies which had already reported that estrogen causes. rather than cures, heart attacks. It causes a magnesium deficiency, which promotes clotting (Seelig and Heggtveit. *Amer. J. Clin. Nutr. 27*, pp. 59-79, 1974). The magnesium deficiency also promotes abnormal fat metabolism, contributing to heart disease. Even before estrogen was chemically identified, it was known to promote breast cancer; in the 1930s it was shown to cause tissue aging, fibroid tumors, various cancers, premenstrual syndrome and menstrual abnormalities, and to induce abortions. Nevertheless, from 1947 to 1964 a synthetic estrogen, DES, already demonstrated to be highly toxic, was prescribed to millions of women to *prevent* miscarriages. When women succeeded in having babies in spite of this mistreatment, it typically caused girl babies to later develop vaginal cancer, and many of the boy babies grew up to be sterile. By the early 1960s it was apparent that birth control drugs had a bigger market than drugs for the miscarriage trade, so DES was switched over to use in birth control pills, and is still widely used as a morning after pill." Since estrogen was known to cause obesity and edema, it occurred to someone that there would be a really big market for DES in the meat industry: chickens, turkeys and cows with edema weigh more, and gross fatness not only increases the animals' weight, it also fills out the skin so the animal looks smooth and plump. (The same effect of plumpness has been sold to women as "young skin," even though estrogen actually causes aging of the connective tissue in skin.) Meat graders have said that DES lowers the quality of the meat (apart from the residue toxicity), but the incresed weight makes it a profitable practice.

By 1950, any normally perceptive person was aware that physicians were doing things exactly backwards in many cases. This was not the result of a new homeopathic philo-

sophy, or the "hair of the dog that bit you" theory. It was the result of drug companies' having their patented products, and knowing how to use the medical establishment for their own purposes, without regard to science. Their huge profits allowed them to spend several thousand dollars each year on each physician, sometimes including gifts of color television sets and free vacations, and discounts on things for the doctors' own use. Probably the most terrible use of their wealth was the gradual reversal of scientific opinion, achieved through grants to scientists who got the results they wanted, and cancellation of grants when the results went the wrong way, and through financial support for professional meetings and publications, and through influence on the editorial policies of medical journals by the threatened withholding of advertising.

Probably the last, strongest argument for the widespread use of estrogen is that it supposedly delays the development of osteoporosis. The absence of osteoporosis in old women in many other countries is never discussed in the professional meetings on osteoporosis subsidized by the drug companies. Constance Martin, in her *Textbook of Endocrine Physiology,* (1976), says that "estrogens are not useful if administered over long periods of time...." M.R. Urist (in ***Biochem. and Physiol. of Bone, vol. II,*** G.H. Bourne, 1972 ed.) says that estrogen doesn't restore bone mass "to a degree demonstrable by roentgenography," that excessive growth hormone "may aggravate" the disorder, and that estrogen stimulates the release of growth hormone. The argument for using estrogen to cure or prevent osteoporosis is based on the fact that estrogen causes diminished urinary excretion of calcium. A vitamin E deficiency (and estrogen is known to increase the need for vitamin E) causes calcium to be retained by muscles. Any toxin, in fact, causes calcium retention in the soft tissues — for example, when the heart is deprived of oxygen, it absorbs calcium. Since no skeletal improvement can be demonstrated by x-rays, I suspect that the improved calcium retention is merely a toxic effect of estrogen. A proper control in this sort of experiment would be to compare the effect of toxins such as iodoacetate and cyanide, with the effect of estrogen.

BLOOD PRESSURE - VITAMIN E AND OTHER NUTRIENTS

The kidneys produce a material which raises blood pressure, and the production of this chemical is increased when the supply of oxygen is not adequate. Other tissues probably produce similar chemicals. Normally, as soon as the blood pressure is increased, circulation is improved so that an adequate amount of oxygen is delivered to the tissues.

However, there are many processes that can waste oxygen, and some of these tend to increase gradually with age, so that the blood pressure rises steadily over the years.

General tissue damage, malnutrition, and hormone imbalance can all produce conditions in which oxygen is consumed without producing a normal amount of energy. Also, a failure of the small blood vessels to open properly can cause oxygen deprivation, as can a tendency to form small clots.

All kinds of stress tend to make the liver sluggish. The liver normally removes toxins and excess hormones from the body. Estrogen can accumulate to high levels if the liver isn't fully active. One effect of estrogen is to promote oxidation of a type which doesn't provide energy, thus raising oxygen requirements. Another effect of estrogen is to inhibit a proteolytic enzyme in the blood, which normally dissolves clots. This is why birth control pills can cause blood clotting, strokes and other circulatory problems. Some of the long-recognized signs of excessive estrogen are vascular "spiders," little red dots that some doctors like to burn off, brown spots on the skin, lumps in the breasts, a slight bluish color in some skin areas, puffiness, dizziness, etc.

Vitamin E promotes oxidation in many ways, and seems to specifically oppose many of the effects of excess estrogen. For example, it can help protect the liver against damage by toxins (all the nutrients are needed by the liver though). It opposes the tendency of estrogen to create "age pigment." It activates the blood protease, and so speeds clot removal and prevents clot formation inside blood vessels, but there is also evidence that it promotes normal clotting in wounds. The products of dissolving the proteins of clots are small peptide molecules called kinins, which act as local hormones to relax the walls of blood vessels, allowing easier flow of blood, better oxygenation, and lower blood pressure. Inside the cells, vitamin E inhibits destructive and wasteful oxidation (such as is involved in aging and cancer) and makes the normal oxidative process more efficient, providing more useful energy for a given amount of oxygen.

One theory of vitamin E action is that it protects progesterone. A recent discovery is that a prostaglandin (a hormone made from fatty acids) regulates blood pressure via the kidney — vitamin E protects fatty acids.

Recently it has been found that some natural vitamin E is contaminated with estrogen from the plant source, e.g., alfalfa.

Part of the reason for the common medical disbelief in the efficacy of vitamin E is that it doesn't work like a drug — a big dose doesn't immediately force the blood pressure down. Sometimes, in fact, the first effect is to strengthen a damaged heart, raising the blood pressure for a few days. But it does

eventually remove many of the causes of high blood pressure, and I have never seen it fail to lower high blood pressure. Synthetic vitamin E is dl-alpha tocopherol, and may be associated with the reports of fatigue and headache from 800 units a day (however, this often repeated rumor is hard to track down — sort of like stories of blindness from vitamin A or LSD). Some "natural" vitamin E brands are contaminated with the petroleum distillate used for extraction, and taste like kerosene; the name d-alpha tocopherol indicates that it has been extracted from natural oils and has the "handedness" (chirality) of most biological substances (d and l mean right and left).

Other vitamins that can improve circulation by opening the small blood vessels are folic acid and niacin. Vitamin C can help to eliminate toxins that could contribute to high blood pressure. Trace minerals (such as those found in kelp and bran) and magnesium should also be considered in circulatory problems. Magnesium acts against calcium (and estrogen) in the clotting system, can prevent spasms of blood vessels, and can spare oxygen.

According to Barnes, nearly all hypertension can be helped with thyroid.

IV. SOME DISEASES

NEARSIGHTEDNESS (MYOPIA)

Many years ago I noticed that my nearsightedness increased when I was under stress. Many people become slightly nearsighted at night, or in the dark. Since the blood sugar concentration decreases at night, and under certain stress conditions, I guessed that myopia might be caused by chronic deficiency of sugar supply to the eye. This idea was reinforced when I read that tears normally contain more glucose than do the other body fluids, and then found that my tears usually had less sugar than the eyes of people with normal vision or with farsightedness. I found that many people (not just diabetic, whose altered refraction is usually blamed on swelling of the eyeball) had experienced very rapid and large changes in their degree of nearsightedness. In young women, I found that it was very common for them to become myopic within weeks of the time they began taking birth control pills, and that their vision sometimes corrected itself when they stopped taking the pill after a year or two. In women who were on the pill, and then began taking thyroid hormone, the thyroxin tended to correct their vision. Since estrogen tends to lower the blood sugar level, and thyroxin tends to raise it, these observations are consistent with the

idea that myopia is caused by a deficiency of glucose in the eye. In the walls of the eyes of chickens, cells which look like smooth muscle cells are present. If smooth muscles in the wall of the eyeball are responsible for maintaining the roundness of the eye, against the near-focus apparatus around the lens, then chronic starvation of those cells would lead to elongation of the eyeball (in proportion to the amount of close work), producing myopia. Besides avoiding the pill, all of the anti-estrogen and anti-stress nutrients should help to prevent the progression of myopia, and being outside in good weather — to promote the tear flow — might even reverse it, as thyroid hormone does.

COLITIS, REGIONAL ENTERITIS (CROHN'S DISEASE), INFLAMMATION, AND FIBROUS DISEASES, AND "COLLAGEN DISEASE"

Stress consumes steroids and produces the many degenerative diseases described by Hans Selye. The gastro-intestinal system becomes inflamed or ulcerated, and fibrous tissue may proliferate. Adrenal glands enlarge, and lymphoid tissue shrinks during the first stage of stress (and may enlarge later). Stress can be produced by dark cloudy northern winters, by inadequate nutrition, by the use of estrogen and many other drugs, and by the use of foods which inhibit the thyroid gland (bakery bread, lacking available manganese and containing iodate and bromate; cabbage family, and many cereals and nuts containing nitriles, cyanide or thiocyanate; meats "refined" from animals whose thyroid tissue is sold to drug companies).

Stress diseases typically have a dominant allergic aspect, and respond to steroids. Cortisone is used medically, but has side effects which could be avoided by using progesterone (though "medical" progesterone usually contains allergenic solvents and "preservatives" such as phenol). **Niacin, vitamin A, vitamin C, etc., help to produce progesterone, and so often help in stress diseases, though** the manufactured substances are themselves somewhat allergenic. (Vitamin A is not usually "manufactured.")

Light deprivation can be remedied artificially, but the necessary brightness is usually underestimated. Because an adequate diet is hard to get in our culture, which makes it *illegal* to sell the thyroid gland as food, it is often necessary to buy this powdered meat in tablet form from your physician and druggist. Meat eaters would normally get ¼ to ½ grain of thyroid in their food every day if the whole animal were used. Eggs, sardines, oysters, chicken stew (non-estrogenized chickens), etc., are examples of "unrefined" protein foods which shouldn't interfere with thyroid function. Vegetarians

often notice temporary exhilaration when they stop eating meat, probably because their thyroid has been suppressed. But a more serious hypothyroid state often follows, from a low protein inadequate vegetarian diet. Low protein diets definitely interfere with the liver's ability to detoxify estrogen and other stressors.

A diet high in animal protein with other nutrients, including an appropriate amount of desiccated thyroid if "refined" proteins are used, can cause an immediate improvement in many diseases which are specifically produced by stress.

HEART DISEASE

There are several reasons to suspect that a magnesium deficiency is often involved in heart disease; in a clinical study, for example, injected magnesium sulphate helped in angina pectoris and coronary thrombosis, and tended to lower blood lipids. Numerous studies have found that a high magnesium intake is associated with low blood cholesterol levels. Magnesium also opposes clot formation and vascular spasm, which can be promoted by an excess of calcium. Estrogen was once used to "prevent" heart attacks, but it is now known to *induce* heart attacks in both men and women. Vascular spasm is now recognized as a cause of heart attacks.

The Shutes have done extensive research on the use of vitamin E in heart disease, and found that "pharmacological" doses of 400 mg/day or more are beneficial. They have also recommended it for preventing thrombosis elsewhere in the vascular system. In problems such as varicose veins and clots in the legs, they say:

> It mobilizes collateral or detour circulation about the obstructed veins in the deep parts of the leg. It is the best and safest agent one can use. It not only melts away the existing clot and helps the inflammatory process to subside, but it hinders extension of that process and almost never permits a part of the clot to break loose and strike some other part of the body, such as the lungs or brain (an accident called embolism). We feel that vitamin E is very effective in preventing thrombosis within the vascular system, and acts more simply, more cheaply and much more safely than the rival anticoagulants.

Other points relating to heart disease are discussed in the section on high blood pressure. Low thyroid is known to be a cause of both heart attacks and of elevated blood cholesterol. (B.Barnes; Adv. in Lipid Res.)

ARTERIOSCLEROSIS

The American Dietetic Association warns about overdosing with kelp. because of the iodide; but the Japanese eat various iodide-rich seaweeds without the thyroid problems the A.D.A. says might occur on the kelp-lecithin-vinegar B6 diet. In the U.S. people who eat bakery bread receive about 10 times more than the RDA of iodine. Iodides are known to benefit arteriosclerosis, with visible improvement occuring in blood vessels in the retina (see *Physicians Desk Reference*, iodides). In old age, the walls of blood vessels tend to become hardened with calcium. In at least some tissues, it is known that calcification begins in degenerating mitochondria, and mitochondria tend to deteriorate in aging tissue. Nutrients such as iodine, vitamin E, magnesium and vitamin B2 are especially important for maintaining the function of the mitochondria, which produce most of our energy. An excess of iodine from bread or kelp is much more likely to interfere with the thyroid when the diet contains a large amount of unsaturated fat, such as safflower or soy oil, because these combine with iodine to form substances which inhibit the thyroid. These oils in themselves suppress the thyroid, and this might be a factor in the premature aging and increased cancer rate which have been observed in people who use larger amounts of those oils.

Atherosclerotic damage (fatty deposits) of blood vessels is made worse by sugar supposedly, since insulin is involved in cholesterol damage. There is evidence that lecithin and other phospholipids protect the body against fatty degeneration. Eggs, for several reasons might actively protect against the formation of cholesterol deposits. One of the men who discovered insulin, Best, later showed that choline (a component of lecithin) can prevent fatty degeneration of the liver. Very large doses of biotin cause experimental animals to develop fatty livers (developing into liver cancer), but this effect can be offset by feeding the animal another B vitamin, inositol. Some of these effects have been known for about half a century, but too many "health professionals" are still pretending that no valid data exist. Maybe we should start asking whether these "health professionals" have a valid existence.

POLIO: A CHRONOLOGY (OR, ISN'T SCIENCE WONDERFUL?)

Muller in Switzerland in 1830 built the steel roller wheat mill.

Jacob von Heine first diagnosed polio, 1840.

First polio epidemic, Sweden, 1887.
Epidemic in some region of U.S. almost every year after 1900.
In 1952, epidemics in Denmark, Germany, Belgium, 33,344 cases in U.S.

An epidemic of rumors that Mexicans didn't get polio because of the absence of white bread and sugar in their country. (Sugar refining developed in Europe roughly parallel with flour refining.) The white flour producers financed research by a Harvard group to find the cause of Mexicans' apparent resistance to polio. The Harvard scientists concluded that Mexicans are so dirty that they are constantly eating the polio virus and so never catch the disease.

According to Harrison's *Principles of Internal Medicine*, polio can be spread by injection, including vaccination. Salk vaccine in many cases apparently brought on polio after the first or second injection in the series of three. Studies in which people were advised to avoid sugar and starch during the (summer) "polio season" never got government or institutional support. However, some studies were done: see the section on infections.

MULTIPLE SCLEROSIS

Roger MacDougall's diet for preventing the progression of multiple sclerosis involves avoidance of gluten and the use of a vitamin-mineral supplement. A letter in *The Lancet* (Oct. 5, 1974) describes one form of the diet: "subject avoids eating wheat, oats, rye and barley...takes less saturated fat, replacing it in part by unsaturated fat, reduces his sugar intake, replacing the remaining white sugar by Barbados sugar, and supplements his intake of food with" the following:

Vitamin B1	24 mg. (per day)
Vitamin B2	12 mg.
Vitamin B6	60 mg.
Nicotinamide	1 gram
Calcium Pantothenate	120 mg.
Vitamin C	600 mg.
Vitamin E	180 mg.
Calcium gluconate	900 mg.
Magnesium hydroxide	900 mg.
Vitamin B12	150 micrograms

That writer suggests that the calcium might not be desirable in the formula. I think the magnesium is extremely important, and it might be better to use it in a more soluble form, such as magnesium carbonate or magnesium chloride, or even

epsom salts (magnesium sulphate) which in large doses can't be absorbed, but in small doses will be partly converted to the chloride by stomach acid. Some people, suspected of having early MS, have been able to stop the symptoms just by avoiding carbohydrates. Biotin is involved in the synthesis of fats in the nervous system, and so should probably be given special attention in the MS diet. Liver is a good source of it. If it is taken as a supplement, inositol (and probably choline) should be taken with it, because large doses of biotin by itself were toxic in animal experiments.

Stress, the immune system, and lipid metabolism have complex interactions. For example, a fat, triolein, is known to stimulate phagocytosis, as does magnesium; sugar in the diet has an opposite effect. Stress increases breakdown of fats, and can decrease the proportion of triglycerides (triolein is a triglyceride, meaning it is composed of glycerin and three fatty acid molecules) in the blood. Avoiding stress (coffee, tea, and other stimulants produce a stress-like reaction in many people) should be part of a multiple sclerosis program.

Steroids have been used apparently to inhibit an inflammatory process, though it was about 1978 before an active brain inflammation was observed in a person who died with MS. Good nutrition would support the synthesis of natural steroids. Hypothyroidism can mimic the neurological problems of MS, but neurologists are generally willing to diagnose a condition as MS without giving thyroid tests. Vitamin A is needed for steroid production and should be added to MacDougall's program. I think beans and nuts should be avoided as well as the grains.

Polyunsaturated oils inhibit the immune system and so probably suppress symptoms. The steroids (e.g., progesterone) and thyroid hormones normalize the immune system when they are present in normal amounts.

INFECTIONS

In the winter of 1974 a young professor visited me to talk about Blake College, and we started talking about nutrition and health. After I told him some stories about antibiotics and vitamin A, he mentioned that he had a chronic, active and uncomfortable infection of the urethra (non-specific urethritis, a bacterial infection of the urinary canal, usually involving E. coli, the common intestinal bacteria, and less often Proteus, Staphylococcus aureus, Enterobacter, Pseudomonas, etc.) for nearly two years. Twice he had been given a month's course of high potency antibiotics, which

suppressed the symptoms while he continued to take them, but the condition returned immediately when he stopped taking the antibiotics. He was interested in trying to nutritionally raise his immunity, so I gave him liver for lunch, and suggested that he eat some daily, and gave him a week's supply of vitamins A, E, folic acid, B6, potassium and magnesium. He was scheduled to come back to town in a week, so I asked him to let me know how he felt then. About a day later, he came back in a very surprised state, and said the infection had already completely cleared up. This spring (1975) he came back and is still free of the infection. This sort of infection is more common in women, and usually takes longer to clear up.

Folic acid, known for its ability to cure some anemias (red blood cell deficiency) also improves the function of white blood cells, improving antibody production. It is also possibly involved in a non-antibody process which allows white blood cells to destroy virus, fungi, and other parasites.

Vitamin A, besides strengthening membranes, is necessary for protein synthesis, and so helps form the immune tissue. Zinc has similar general functions in protein antibody production, but also possibly has a direct "viricidal" capacity, as observed *in vitro*, which would account for its release (and loss) during viral infections. Vitamin A (and possibly folic acid) mediate the body's response to light, and so modify its neural control of immunity, thyroid and adrenal and sex hormone function, etc.

Unsaturated fatty acids inhibit some immune functions and also inhibit the thyroid gland and directly inhibit cellular respiration. As Broda Barnes has pointed out, hypothyroidism predisposes people to infections; chronic respiratory, ear, and bladder infections are common results.

Vitamin C increases the structural strength of the mucous membranes' connective tissue, in proportion to its intake, up to the megadoses recommended by Pauling (according to electron microscope evidence, *J. Clin. Nutr.*, summer, 1974). It is also more concentrated in white blood cells than in any other tissue (about a 60 to one ratio between white blood cells and surrounding fluids), and their immune function depends on its presence in adequate amounts. Up to 200 mg. daily intake, vitamin C concentration in blood and tissues increases rapidly, and the kidneys work to reabsorb it; at about that intake, the kidney's ability to conserve it becomes "saturated", so that higher doses are retained at lower efficiency. The increased body retention of vitamin C when 5 grams per day is taken is about 4 times that of 100 mg. per day.

Zinc and vitamin A may also act through the blood sugar. It is well known that an emotional upset, spending too much time in the sun, working too long without eating, etc., can bring on an attack of herpes ("cold sores", for example): low blood sugar probably precipitates the eruption. Polio outbreaks always occured in the summer when people tend to eat more carbohydrate (because of the lower specific dynamic action, relative to protein — it heats the body less for a given amount of energy). B.F. Sandler wrote a book on nutrition for avoiding polio (H.G. Muller-Verlag, Krailing bei Munchen, 1959) in which he claimed that infection with the polio virus is only possible if the blood sugar goes below 80 mg. per cent. If this is true of the herpes virus, it would suggest a reason for the association of cancer with both herpes and estrogen, since estrogen lowers blood sugar, and both the virus and estrogen can cause tissue irritation and cell division. Vitamin A is being used experimentally to prevent cancer and to reverse precancerous conditions, especially in the cervix and the mouth. Many women have premenstrual herpes outbreaks which can be controlled with progesterone or thyroid.

P. Delbet used physiological magnesium chloride (12.1 grams per liter) to stimulate phagocytosis in white blood cells. The activity was more than doubled by injection of 150 cc. of this solution into a dog, or by application to cells in vitro. (See *Magnesium: the Nutrient that Could Change Your Life*, J.I. Rodale, Pyramid, New York, 1968.) Dr. U.D. Register, of the School of Health at Loma Linda University, has done related work that shows a decline of white blood cell activity with increased sugar in the diet.

FOOD ALLERGIES

Cooking, by altering the proteins, can lower the allergic reaction to many foods. Soaking seeds before cooking them can have the same effect. Storing foods such as seeds in a sealed bottle in the refrigerator will slow the deterioration of oils, and rancid oils can be very toxic and irritating. Many people lose their allergies (even hay fever and poison-oak sensitivity) when they take supplements of the vitamins A, C, and pantothenic acid.Plants evolved special toxins to protect their seeds from animals, so "seed poisoning" is probably a more accurate description than "allergy to grains, nuts,

Heat will destroy some seed toxins, but it also creates

new poisons and damages the protein quality. For example, heat cause lysine to react with sugars, forming a carcinogen.

Plants evolved special toxins to protect their seeds from animals, so "seed poisoning" is probably a more accurate description than "allergy to grains, nuts, legumes, seeds." Low thyroid function leads to poor digestion and to hypoglycemia, both of which make an allergic reaction more likely.

A NOTE ON GLAUCOMA

Because of their stress-like effects, coffee and tobacco should be avoided in glaucoma. The nutrients that are especially involved in the adrenal stress reaction should be used: ascorbic acid, pantothenic acid, riboflavin, vitamin A, magnesium, and vitamin E.

Progesterone (natural form) is a diuretic and also is a precursor for the anti-stress hormones, and sometimes helps glaucoma. The nutrients mentioned above promote its synthesis. Estrogen blocks its actions, so it would seem desirable to avoid estrogen, and to use the nutrients which oppose estrogen.

The eye itself has especially high requirements for vitamins A, B2, and niacin, and coenzyme Q.

Salt and water metabolism involve vitamins B6, pantothenic acid, A, C, E, and niacin (see R.J. Kutsky, *Handbook of Vitamins and Hormones,* p. 263), and various minerals (other than sodium) including magnesium, potassium and zinc.

Because of the role of carbon dioxide in circulation, vitamins B1, B6, and biotin, and zinc, should also be considered. Choline is now known to stimulate acetylcholine synthesis, and so might help to promote a normal parasympathetic innervation.

INSOMNIA

A few weeks ago a woman, in her 40s and taking estrogen pills by prescription, was complaining of extreme insomnia and other symptoms. I suggested that she might be getting too much estrogen, so she stopped, and immediately was able to sleep normally. Sometimes a few hundred milligrams of magnesium carbonate per day (or a spoonful of epsom salts, if this dose is divided into several parts to avoid the laxative effect) will immediately make it possible to sleep normally. Zinc, as in oysters, and potassium and the B complex vitamins, as in brewer's yeast, are sometimes necessary. Many people get gas from the complex carbohy-

drates in yeast. This can be prevented by steeping a tablespoonful in a cup of boiling water, and drinking only the yellow liquid and throwing away the sediment. Protein is lost, but the other nutrients are highly soiuble. Milk contains natural sleep-inducers, including the amino acid tryptophan and milk sugar. Two or three tablespoonfuis of honey in a glass of milk will provide some magnesium, as well as sugar to increase the liver's stored glycogen. When blood sugar is low, adrenalin is secreted to raise the sugar level, but it also tends to keep the person awake, by causing nightmares, sweating, rapid heartbeat, etc. Since blood sugar is normally higher in the daytime, because of light's effect on various glands, some people with defective livers find it easier to sleep in the daytime. Hypothyroidism is the most common basic cause of low blood sugar, and very commonly causes insomnia. I have noticed that "bedtime worries" are associated with hypothyroidism, and disappear when it is corrected.

Although tryptophan supplements are available for insomnia, I think its chronic use would be as dangerous as the tranquilizer, reserpine, which acts on the same biochemical system, and which increases the risk of breast cancer.

LOW BLOOD PRESSURE

Some doctors say that lower than average blood pressure is a good thing. Many women have a systolic pressure of around 100, and I think rightly suspect that it relates to their feelings of weakness or fatigue or even dizziness. Sometimes orthostatic hypotension, the failure of blood pressure to rise when the person stands up, is described as "dizziness." A relative deficiency of the catecholamines can produce these symptoms.

For several years I had suspected a connection between estrogen and low blood pressure, just from noticing that women with seemingly high estrogen tended to have lower than average blood pressure. The fact that estrogen, acting as an antagonist to vitamin E, could promote high blood pressure had distracted my attention from the opposite effect, being produced by an antagonism to thyroxin. It was enough of a heresy, for the moment, to point out the many ways in which estrogen antagonizes thyroxin; in addition to things I have mentioned elsewhere, I think the opposition is also visible in the action of estrogen on blood lipids. Since aging and x-rays have some biochemical effects similar to those of estrogen, they might also antagonize thyroxin; this suggests that large doses of thyroxin might be used in senility, radiation sickness, and cancer.

Since thyroxine potentiates adrenalin, which maintains blood pressure, excess estrogen, antagonizing thyroid, could tend to lower blood pressure through this system. The thermogenic effect of progesterone might act by way of thyroxin; if so, it might be the best way of counteracting estrogen and promoting thyroxin activity. The opposite reaction to high estrogen-low thyroid is also known to occur: an elevation of brain catecholamines and also an elevation of blood pressure. Thus, a thyroid supplement can often correct hypertension, as well as hypotension.

SKIN FEEDING

Oily things enter the body very easily through the skin. Toxic solvents should never touch the skin. just as they never should be breathed. Oily vitamins and hormones can be applied to the skin. There is a form of vitamin C (ascorbic palmitate) which enters the skin quickly. and according to the Soviet researchers who developed it. can be used to carry other nutrients in through the skin. Significant quantities of fat (such as olive oil) can be given by massage when the person is too sick to eat. For years people have noticed that zinc oxide ointment speeds healing, just as zinc in the diet improves healing. Zinc chloride dissolved in vegetable oil was found to raise blood zinc very effectively when painted onto the skin. Zinc has been used successfully to treat stretch marks. Probably other minerals will enter the skin as easily — magnesium sulphate (epsom salts) is a traditional treatment for inflammations. Since carbon dioxide dissolves best in "oil loving" material such as the skin, it enters the body even against a concentration gradient. Adding baking soda to an epsom salts soak should make it more effective. Mineral oil, vaseline, and rancid vegetable oil should not be put on the skin. Lotions and other cosmetics generally contain mineral oil.

IDENTIFYING DEFICIENCIES

Frequent nosebleeds, bloodshot eyes. and visible blood vessels on the cheeks and nose can be symptoms of a deficiency of vitamin B2. Vitamin C, rutin. and iodide are other nutrients that can sometimes correct blood vessel problems.

A peculiar kind of irritability, sometimes with a sense of having your head in a kind of "cloud", is often a result of a vitamin B1 deficiency. If that is the cause. it will clear up within a few minutes after taking the vitamin. Magnesium deficiency is another common cause of irritability.

White stripes across the finger-nails, especially on the right hand, seem to represent a zinc deficiency. Menstruation can cause loss of zinc, so that some women have five or six spots evenly spaced up the length of the nail, each resulting from one period. The length of the nail represents about six months' growth. A virus infection can have the same effect. The eyebrows sometimes become bristly in a zinc deficiency. A zinc deficiency is often associated with a deficiency of vitamin B6 and an excess of copper; since estrogen is associated with zinc loss, other nutrients including vitamin E and folic acid should be considered when the nails have white marks.

Sore spots at the sides of the mouth often result from a vitamin B2 deficiency; other B vitamin deficiencies can cause a sore tongue, and a niacin or protein deficiency can show up first in the gums as tenderness or bleeding. (A thyroid deficiency contributes to receding and bleeding gums, pyorrhea, etc. A recent book on Ubiquinone, coenzyme Q, shows that gums heal rapidly when the person consumes a ubiquinone supplement. This nutrient is found in heart, liver, greens, etc., and is closely related to both vitamin E and thyroid hormones.)

Teeth that are sensitive to heat or cold suggest a deficiency of calcium, magnesium, or vitamin D. Blood sugar and calcium seem to be related, and a dental researcher has shown that teeth are sensitive to alterations in the blood sugar concentration. Cramps, especially in the feet and legs can result from a deficiency of these same nutrients.

Weak fingernails are common in protein deficiency and hypothyroidism. Falling or very fine hair also suggest hypothyroidism, which can result from stress or eating anti-thyroid foods. Many other symptoms are discussed in sections on progesterone, thyroid and estrogen.

WARBURG'S CANCER THEORY, CACHEXIA AND THYROID THERAPY

Warburg[1] demonstrated that all cancers have defective respiration, by which he meant that glucose is consumed too rapidly. The excessive consumption of glucose in the presence of oxygen is called aerobic glycolysis, and is typical of cancer. Oxygen may be consumed, but it does not result in the production of sufficient ATP to inhibit glycolysis (by the Pasteur effect). This generally means that excess lactate will be produced and will leave the cell, will be detected by other tissues, and will be processed by the liver into glucose. Lactate is a sufficient stimulus to trigger the stress reaction, and in

many people causes an anxiety syndrome. Since resynthesis of glucose from lactate by the liver requires much more energy than is derived from conversion of glucose to lactate, the tumor's formation of lactate consitutes a large energy burden to the organism. Total energy consumption would increase, because of intense but inefficient metabolism in the tumor and in the liver, and also possibly because of stress-induced brain excitation and the catabolism of muscle and other tissue proteins. Cortisone elevates blood glucose and would inhibit the thyroid. Since there is evidence of thyroid deficiency in various cancers, and since thyroid supplementation reduces the incidence of spontaneous tumors, thyroid therapy would be desirable in cancer, especially if there is cachexia. Gerson[2] and Tallberg[3] have reported good results from using thyroid as part of supportive therapy.

The stereotype of the hypothyroid person as overweight will lead the typical physician to believe that metabolic stimulation by thyroid would be exactly the opposite of what the cachectic patient needs. The relevant effects of thyroid (especially with protesgerone, to promote tissue response to thyroid, and to block cortisone production) however, are stimulation of protein synthesis and the prevention of lactate formation - or the stimulation of its oxidation, either by the tumor itself or by other tissues, to prevent its entry into the Cori cycle, for gluconeogenesis. (Cachexia strumipriva should be kept in mind).

Warburg believed that a riboflavin deficiency was an important contributor to the development of defective respiration, but he also pointed out that the simple lack of oxygen would promote the development of cancer. I have emphasized the role of estrogen in creating an oxygen deficiency. Since it inhibits the secretion of thyroxin at the glandular level, and antogonizes thyroxin at the cellular level, estrogen is a good candidate for the main cause of the respiratory defect. It also antagonizes other respiratory factors, such as magnesium and vitamin E, and radioactive estrogen has been shown to accumulate selectively in (liver) cancer cells. (And excess estrogen actually impedes oxygenation of the blood.)

Once we accept Warburg's thesis, that damaged respiration is the prime cause of cancer, the therapeutic use of thyroid in cancer seems obvious. Schizophrenics seem to have either a resistance to thyroid hormones or an inability to convert T_4 to T_3. Aging and estrogen-dominance are other states in which cells seem to be relatively insensitive to thyroid hormones. If the liver is a main site of T_4's conversion to T_3, cancer patients may require very large doses of thyroid, or else direct use of T_3 (possibly in large doses), since the liver is so likely to be inefficient.

[1]Otto Heinrich Warburg, **The Metabolism of Tumors,** R.R. Smith, Inc., New York, 1931.

[2]Max Gerson, **A Cancer Therapy,** Whitier Books, New York, 1958.

[3]I. Tallberg, **Protides of the Body Fluids,** 1978.

CANCER, STRESS, AND NUTRITION: A SUMMARY

Cancer lives on sugar. It disturbs metabolism, tending to lower blood sugar (even to the point of causing hallucinations) and promotes the conversion of good tissue into sugar: the liver and the immune tissue are the first to show this effect. Stress first elevates adrenaline, which causes fear and anxiety; adrenaline then stimulates the body to produce cortisone. If nutrients, especially vitamins C and A, are available the adrenal glands will produce cortisone to maintain the blood sugar as long as some good body tissue remains to convert to sugar, unless adaptation occurs.

If the body can adapt to get most of its energy from fat oxidation, then blockage of sugar metabolism can lead to starvation of the cancer. A magnesium deficiency damages energy production and leads to high sugar consumption, with the associated tendency to destroy protein. During healthy adaptation to fasting, the body consumes fat preferentially — the brain is usually the biggest consumer of glucose, and it can adapt in about two weeks to oxidize mainly fat, as ketones. In this state, the kidneys (as well as any cancer) will consume protein and produce ammonia and fuel; the kidneys synthesize glucose (estimated at roughly 40 grams per day) from the protein, but the reason for this reaction seems to be the need for ammonium ions to balance the keto acids which are being eliminated in the urine. If the need for positive ions regulates this conversion of protein to

glucose, then the wasting of the body and the production of glucose could be reduced even more by providing positive ions — as carbonates, or carbonate precursors to be chosen by their tendency to stimulate respiration rather than gluconeogenesis (possibly citrate or acetate, though acetate might inhibit lipolysis; these anions would be needed in such small amounts that their effects might be negligible). The cations would be chosen for their ability to regulate many aspects of metabolism, including glycolysis, respiration, hormone secretion, and immunity. They would include, in order of probable quantities, magnesium, zinc, manganese, and molybdenum. Certain fruits probably approximate the ionic balance needed.

Very high elevations produce hormonal and metabolic adaptations which are appropriate for recovery from cancer. (See S. Tromp's *Medical Biometeorology*, and F.Z. Meyerson's work in the Soviet Union.) Even moderate increases in elevation lower the cancer rate (see references in my article on the "excitable ether").

Vitamin A is needed for proper differentiation of various types of cell, and has been used successfully in blocking cancer formation and in causing precancerous tissue to return to normal. Progesterone "spares" vitamin A, and has been used in cancer therapy. Iodine has a long history of use in cancer therapy; the tissue lump produced by tuberculosis bacilli has some similarity to tumor formation in cancer (this was an idea behind the use of a harmless form of the tuberculosis organism, BCG, in cancer therapy to stimulate the immune rejection system). Iodine was found to restore activity to proteolytic enzymes which are inhibited by TB, and allow dissolution of the nodule. Progesterone and vitamin A interact with the thyroid hormone; when body temperature is below normal there is typically a progesterone deficiency (or estrogen excess, which may be functionally equivalent to a thyroid deficiency). Normal inhibitors of cell division (chalones) are not retained in cells at a normal level when ATP and vitamin E are deficient. Rapid growth is obviously one factor which could make it difficult to obtain adequate levels of some nutrients, such as the oily vitamins A, K, E, and D, just as wasteful use of oxygen can rob adjacent tissues and lead to spreading of the inflammation. ATP normally circulates in the blood in amounts reflecting cellular efficiency. Just as rigor mortis can be softened by injection of ATP, the hardness of a tumor probably reflects ATP deficiency (softening of cervical tumors was observed during progesterone treatment). Intravenous ATP (it could be purified by patient's own serum proteolytic enzyme before use to avoid immune reaction) should be considered as part of a physiological therapy. Magnesium salt of ATP is the appropriate form.

Intravenous ethanol prevents protein wastage without providing glucose to feed cancer; it controls pain as well as morphine with less toxicity. It can also be used as a skin rub, again bypassing the liver. Magnesium carbonate can be given by any route, though it would have to be buffered intravenously. (5% ethanol has been used intravenously, safely.)

Pyrroles and porphyrins in blood and urine, if elevated, suggest that therapies should continue, even if symptoms have disappeared.

Nutrition through the skin can be significant in cancer: oils, vitamins, and minerals go into the skin easily, especially when they are applied in an oily medium.

THE CERVICAL CANCER SCARE

Many women with abnormal Pap smears, even with a biopsy showing the so-called "carcinoma *in situ*," have returned to normal in just two months with a diet including the following: 90 grams of protein, 500 mg. of magnesium as the chloride, 100,000 units of vitamin A, 400 units of vitamin E, 5 mg. of folic acid, 100 mg. of pantothenic acid, 100 mg. of B6, 100 mg. of niacinamide, and 500 mg. of vitamin C, with thyroid and progesterone as needed. Liver should be eaten twice a week. Some of the women apply vitamin A directly to the cervix.

ASTHMA, MIGRAINE, PSORIASIS

During LSD research, it was noticed that people with chronic headaches, asthma, or psoriasis sometimes recovered completely during treatment with frequent doses of LSD. Another alkaloid derived from ergot, bromocryptine, is now being used to suppress lactation (such as is caused by prolactin-secreting pituitary tumor which develops after using oral contraceptives) and is used experimentally to treat Parkinson's disease. Both LSD and bromocryptine shift the ratio of two brain chemicals, DOPA and serotonin, towards DOPA dominance. Among the effects of this is an inhibition of prolactin secretion. Prolactin excess is involved in breast cancer and in other cell proliferation, probably including the rapid cell division in psoriasis. Prolactin apparently inhibits progesterone production, and so could establish a self-stimulating vicious circle. All of the effects of prolactin excess (including amenorrhea) which respond to an increase of the DOPA/serotonin ratio can be obtained to some extent by other, more easily available, materials. Vitamin B6, thyroid, and progesterone all have this action. Nickel has

been found to have this effect in animals, but isn't available as a nutritional supplement. Thyroid and progesterone have relieved asthma, migraine and psoriasis (or eczema) very effectively. Since tryptophan, an amino acid which is being promoted as a sedative, causes an increase of serotonin in the brain, it should not be used as a supplement by people with any of these "low DOPA" symptoms. Milk is a rich natural source of tryptophan. Since tryptophan promotes formation of serotonin which stimulates release of prolactin, and prolactin activates the formation of sebum (oil) by the skin, large amounts of milk could promote a tendency toward acne, when there is a deficiency of B6, thyroid, progesterone, etc.

Although the prolactin-secreting pituitary tumor was very rare a few years ago, it is now the most common form of pituitary tumor. In the 1930's Korenchevsky demonstrated that estrogen produced that kind of tumor, among many others, and that the tumor would regress under the influence of progesterone. Since the liver requires adequate protein to eliminate estrogen, a low protein diet or other deficiencies would undoubtedly contribute to the development of this tumor in a user of birth control pills. Estrogen stimulates cell division in the prolactin-secreting part of the pituitary, and elevates the level of serotonin, and so can be the basic chemical cause of these various symptoms. Diet, stress, and amount of light, of course, can modify the level of estrogen and its actions. The avoidance of anti-thyroid foods such as soy beans, cabbage, and peanuts would be especially important.

V. PREGNANCY AND CHILDREN

AGE AND PREGNANCY

Women are often encouraged to have their children while they are young, by the fear of having a Mongoloid baby (Down's syndrome), which happens more often in older mothers. But someone did a study that showed that Mongoloids are borne more often by women who have been married longer. Women who marry at 30 or 35, for example, were found to have fewer Mongoloid babies than women of the same age who had married younger. The investigator suggested that long-married couples so seldom made love that the chances were greater for the egg (or egg and sperm both) to deteriorate before being fertilized.

Other studies show teen-age mothers have babies with smaller brains than average, and with a greater chance of being slightly retarded. (Smoking during pregnancy has the

same effect; carbon monoxide in city air would probably contribute to the damage.) If women are encouraged to have babies younger, will the population have smaller brains?

Diabetic women are known to typically have large babies with big heads. who learn quickly. With each pregnancy, a woman tends to have less "glucose tolerance," or to seem more diabetic. HCG, the hormone which helps sustain pregnancy, raises the blood sugar to meet the fetus's need for abundant sugar. So diabetes and pregnancy have much in common. And as a woman gets older she tends towards diabetes, and so tends to nourish the fetus better, especially its brain. Besides this natural tendency, a more mature woman is less likely to live on snack foods.

The results of these studies indicate that later marriage would help to reduce the number of mentally retarded children. And better nutrition before and during pregnancy and nursing makes a great difference in the baby's mental and physical development. Young women who are pregnant should be especially careful to avoid low blood sugar. Older women will probably require a little more vitamin E, and should be especially sure that they aren't getting a toxic amount of copper from their water supply or utensils. Regardless of age, pregnant women should make a special effort to get perfect nutrition every day, and to avoid poisons. including drugs, fumes and smoke. Even drugs which don't enter the fetus directly can affect its health by disturbing the mother's metabolism. Many drugs (and food additives) can increase a person's nutritional needs, for example by increasing the rate at which vitamin C is lost in the urine.

Recently there has been a great increase in sterility from endometriosis. Delayed reproduction is a suspected factor. A progesterone deficiency has been implicated. Thyroid, protein and vitamin A help to maintain progesterone production. Alcohol and other drugs used by the father can also cause birth defects.

PRECOCIOUS BABIES

Too much estrogen, insulin, unsaturated fats, or other things which tend to lower blood sugar (toxins including copper, stress, etc.) can lead to mentally retarded babies, premature and underweight babies, and small brained babies. Factors which help to maintain blood sugar, including good diet and hormones such as thyroxin and progesterone, help to produce big, healthy, large brained and precocious babies.

During the last few months of pregnancy, there is often a craving for sweet things, which should be satisfied with fruit. The potassium in fruit has an effect like that of insulin, so that

sugar from the fruit can become available to cells without over-stimulating insulin secretion. Since insulin persists after disposing of excess sugar, it tends to keep blood sugar low and to intensify craving for carbohydrates. Pantothenic acid helps to destroy insulin; this is one way it helps to maintain adequate blood sugar levels.

During pregnancy the mother's body adapts to live increasingly on fat, so that most of the sugar which is available can be used by the baby. The brain uses most of the body's glucose, so mental fatigue can easily affect the blood sugar level. The developing baby is extremely dependent on glucose for its energy supply, and its brain can be damaged by sugar starvation.

Women who are mildly diabetic are known to have big, precocious babies with large heads. Pregnancy itself resembles diabetes, in the adaptation to oxidizing fat rather than sugar, so that a slight tendency toward diabetes can be thought of as a support for pregnancy. Older women are more likely to have some degree of "diabetes," or elevated blood sugar. With each pregnancy, there is a tendency for the blood sugar to be higher, and for the baby to be bigger and more precocious. Older women, in fact, tend to have superior babies. However, after several pregnancies, especially if they are spaced so closely that the body doesn't have time to recover from the depletion of nutrients, the average birth weight suddenly falls, and problems of cell division such as twinning or Down's syndrome become much more common. The fact that the fourth or fifth baby is always borne by an "older" woman has led to the mistaken belief that age alone is responsible for "mongolism." The essential role of nutritional depletion is shown by comparing birth weights and birth defects in women of different social classes and incomes: at a given age, birth weights are lower and birth defects are more common, and the symptoms of depletion (loss of teeth, decreased birth weight, infertility) occur sooner in poor classes.

Vitamin E, vitamin A, and magnesium are other nutrients that help to maintain blood sugar. Vitamin B12 is needed to use vitamin A. Folic acid, vitamin B6, and zinc are depleted by elevated estrogen and are especially important for healthy pregnancy. Too much copper can lower blood sugar; too much iron can destroy vitamin E, and vitamin E deficiency can lead to jaundice, which can affect the baby's brain.

NUTRITION-RELATED IDEAS FOR MOTHERS

If you are sick, reconsider everything you are doing as a contributing factor. There is an ideology about sickness being "eliminative." This tends to produce some confusion,

about sickness being healthy.

Give yourself time to get entirely well before getting pregnant. C. Brown-Sequard bred injured guinea pigs and found that the offspring had a high rate of epilepsy and birth defects. Sickness or trauma — including surgery — can bring on a chronic state of stress, which involves depletion of many nutrients. A few months of extra nutrition and avoidance of new stress can restore the body's reserves.

Pregnancies should be spaced — 2 or 3 years is usually adequate — to allow the body to replenish itself with nutrients and new tissue.

Studies have been done of the parents of very outstanding people, and on the average the parents were several years older than the general average. Both social and biological factors are involved. Studies of the biological factors suggest that the optimum age range for the mother is between 27 and 37. In higher social classes, with better environmental support, the average baby is heavier, healthier, and more alert, and has a higher probability of surviving to adulthood; the optimum age increases as income goes up. That is, in Guatemala the safest age for both mother and baby might be 19; in the U.S. ruling class, it might be 39.

On the average, each baby up to the 4th or 5th is bigger and healthier, but then there is a sharp decline in the average; it is at this point — which suggests that reserve nutrients have been depleted — that twinning and Down's syndrome become more likely. The mother's teeth also tend to fall out at that point. Calcium and vitamin B12 are centrally involved in the "apparatus" of cell division. Close spacing of pregnancies, poor nutrition, stress and toxins including alcohol and smoking are all known to increase the rate of birth defects.

Anxiety, as in "schizophrenia," decreases uterine blood flow; it is known that women who become pregnant while they are "schizophrenic" selectively abort the more fragile male embryos. The orgasmic pleasure state is not compatible with anxiety, and would seem to guarantee a better blood (and thus nutrient) supply. Good sexual attitudes probably optimize trans-placental nutrition.

Alcoholic fathers seem to produce as many birth defects as do alcoholic mothers. There are probably other more subtle nutritional effects acting through the father, but so far there isn't much clear information on this.

The mother's brain and the mother's liver both seem to make specific contributions to the baby's nature. Both have profound effects on the ability to make sugar available for the development of an optimum baby. Estrogen is regulated — centrally or crucially — by the liver. Estrogen, progesterone, iodine, sugar and stress are closely linked with each other,

and with brain development.

Copper and iron can be toxic. Pregnancy and nursing increase all nutritional requirements, with the possible *exception* of vitamin D, copper and iron; it seems to act like vitamin D, improving calcium deposition. Calorie intake should increase slightly (e.g., 200) in pregnancy, and considerably in nursing (e.g., 1000). Zinc, folic acid, B12, and probably B6, and vitamin E, requirements are increased more by pregnancy than by nursing, while protein, other B vitamins, calcium, iodine, and probably magnesium, vitamin A, and possibly fats, are needed in larger amounts for nursing.

IRON SICKNESS

Iron pills and tonics are a big American institution. Doctors often routinely prescribe iron on the same day they determine that a woman is pregnant. Iron pills are known to frequently upset the stomach, but not many people suspect that "morning sickness" could be iron poisoning. The recommended daily allowance of iron for women is about 18 milligrams, but I have seen advertisements in medical journals for pregnancy pills containing several times that dose, without any warning of possible dangers. It is known that excess iron accumulates in the liver, since there is no mechanism for excreting it. It has been noticed that infections, such as malaria, are higher in people who are getting an iron supplement. In tests *in vitro*, iron damages the capacity of antibodies to destroy germs. In the body, iron appears to be "hidden away" during infections, because of this effect on the immune system.

Since iron dosage is so often increased during pregnancy, we should know the scientific background of experiments on animals. All mammals that have been studied need vitamin E in order to get pregnant and to maintain the pregnancy. About 1940, laboratory animals being fed a commercially manufactured diet started showing signs of vitamin E deficiency, dying of softening of the brain. The manufacturers knew they had added vitamin E to the mixture, but when they tested it they found that it contained none at all. It turned out that the iron salts which were added to the food destroyed the vitamin E. The same process can happen in the intestine when iron pills are taken with a normal diet. Natural sources of iron, such as red meat, wheat bran, wheat germ, or molasses, don't seem to have this destructive effect on vitamin E, so if an iron supplement is needed during pregnancy these foods would seem likely to lower the risk of a vitamin E deficiency and of dangers such as a miscarriage.

Iron pills are often used to treat anemia. There are

situations in which iron pills could make anemia worse, or even be the cause of it. In a vitamin E deficiency, red blood cells become fragile and break. This type of "hemolytic" anemia is fairly common in premature babies, and is now treated with vitamin E. But anemia is too often treated in adults with the routine iron pills, without considering whether the anemia involves fragility of the red blood cells that might be made worse by iron pills that destroy vitamin E. Old people and cancer victims are known to have abnormally fragile red blood cells. Since estrogen seems to oppose some of the functions of vitamin E, it would seem reasonable to consider the role of vitamin E in anemia, before giving a woman iron pills.

Hypothyroidism is a common cause of anemia, possibly acting through the simple mechanism of lowering body temperature so much that blood production is retarded.

FERTILITY

Avoiding anti-thyroid foods, increasing use of eggs and milk; also, possibly liver with thyroid, progesterone (especially when miscarriage is threatened), magnesium, and vitamin E.

BREASTFEEDING

Several years ago in a biology course we were talking about immunology and I learned that proper American biologists "knew" that the mother's antibodies, though present in milk, were all destroyed by the baby's digestive enzymes, and so couldn't possibly offer the baby any immunity against infections. However, I knew that Rumanian scientists, and other unacceptable types had demonstrated that milk antibodies do confer immunity, and that various dietary proteins can enter the body undigested. About 1973, some Americans began discovering that human milk is good for human babies, and helps prevent diseases. It is not going to be so easy now to convince American women that the best nutrition for their babies comes from a "formula," of cow's milk, sugar, and vegetable oil. But foreign babies are still being killed by American companies that dress their saleswomen in nurses' uniforms to convince poor women that their babies need the scientific American "formula," even when there is no clean supply of water to mix it with. Since dietary proteins can get into the blood, early feeding of non-human milk would seem most likely to promote the development of allergies.

Proper development of the face, including the shape of

the jaws and alignment of teeth, is promoted by normal nursing, and interfered with when the baby is fed from a bottle. Extensive studies (such as that done recently by J.W. Prescott) show that pleasurable skin stimulation is extremely important for proper psychological development: brutality, rape, religious activity and competition are high in societies which don't give physical affection to infants. Among other animals, even momentary separation following birth damages social behavior. Prescott criticizes bottle feeding, and refers to Aristotle's belief that the state of mind is dependent on the state of the body: "the care of the body ought to precede that of the soul," and "Therefore, the highest good is some sort of pleasure..." (By 1979, human milk is starting to be accepted as the correct food for babies. What is still resisted is allowing the mother and baby to remain in contact, with no separation following birth.)

BRAIN DAMAGE AND THE PUBLIC HEALTH PROTECTORS

Until the late 1950's, boric acid was still in general use as a "safe" antiseptic, and nursing mothers were advised to use if for "cleaning" and "disinfecting" their nipples, so their babies would be protected from germs. Then a columnist reported that some babies had died from getting too much boric acid with their milk, and that smaller doses could cause nerve and brain damage. This publicity discouraged some of the most dangerous uses of boric acid, but the last time I noticed the contents of Listerine mouthwash, boric acid was still included.

In the early 1950s, hexachlorophene started being used by U.S. hospitals to wash newborn babies. Recently, experimenters washed newborn monkeys in the same way, and found that it was being absorbed and was causing gross brain damage. For twenty years, Americans had kept themselves and their children clean-smelling with phisohex and lifebuoy soap, in the belief that hexachlorophene was harmless. How much dyslexia, hyperactivity, and "minimal brain dysfunction" has resulted from such chemical pseudo-cleanliness? Brain damaged animals are known to become aggressive; could poisoning be a cause of human agressiveness?

A few years ago J.W.Olney of Washington University School of Medicine found that large doses of monosodium glutamate cause brain damage in baby mice, but that the effects aren't obvious until they start to grow up. A typical effect of this kind of brain damage is that the females lose interest in sex and become obese. Since young animals are most susceptible to injury, he criticized the manufacturers who added it to baby foods to make the taste appealing to the

mothers who had become accustomed to the taste of MSG or Accent. As a result of the public concern about monosodium glutamate, the baby food companies announced they were no longer adding the substance; instead they quietly substituted another amino acid with a similar flavor. Olney has demonstrated that other amino acids, such as aspartic acid, can be just as poisonous as glutamate. The FDA takes the line that he hasn't proved MSG to be toxic to human babies.

Now the FDA has given its approval to a new chemical sweetener, aspartame, which is a molecule containing aspartic acid. An FDA scientist said, "We do not deny that certain doses of aspartic acid produce brain lesions..." but "Everything has its toxicity: under abnormal conditions, water can be toxic." Stanley Glassner, a "consumer-safety officer" in the FDA, expresses his concern in these words: "..on the practical side, I wouldn't say everybody should substitute it in their diets." "Sugar has been around for years, and nobody is dying from it. Any new substance, despite all the safety tests, is surrounded by question marks." Of course, there are many studies that contradict his claim that nobody is dying from sugar, but the most interesting thing is how these men argue, as if sugar or water had anything to do with the subject — we don't want the FDA to regulate sugar and water, so we shouldn't ask them to regulate a fine new product for which consumers will pay a "premium price." The FDA calculated the allowable amount of aspartame on the basis of adult body weight; the allowable amount would have to be smaller if a child's body weight were used as the basis. But the foods that can contain it under the FDA guidelines are foods that children normally eat: sweet breakfast cereals, chewing gum, puddings and gelatine, toppings, and dry bases for drinks, as well as in powder or tablet form. In the form of a "table substitute for sugar," it seems that it would be easy for a child to get a toxic dose.

Since Olney has shown that glutamate and aspartame have an additive effect ("half a dose of each equals a full dose of one alone"), children who ate food containing MSG would have a significant chance of going beyond the so-called "safety margin" for aspartame. The FDA chooses to ignore Olney's clear evidence that these two amino acids have an additive toxicity. Beyond this known menace (though no one knows whether humans are more sensitive or less sensitive than mice to these poisons) there is the possibility of their toxic interaction with other food additives. Food additives are not the "traces of chemicals" many people suppose: for example, nearly half of the calcium contained in commercial bread may come from the dough conditioner and mold inhibitor, with the rest being provided

by the milk and wheat. And there are always impurities in the additives, resulting from the industrial processes of their manufacture, but the FDA normally likes to ignore these. When evidence was presented showing that saccharine can cause cancer, the FDA suddenly remembered the impurities in food additives, and now asked for proof that it was "the saccharine itself" that caused cancer, and not an impurity in it. Of course the consumer eats the impurities with the saccharine (and with all other additives), and probably wouldn't care very much whether it was the sweetener itself or the arsenic, mercury and lead in it which caused his cancer. Periodically, women's hair is found to be loaded with arsenic, and the soap companies are told to spend a little more money to remove some of this contaminant, but the pressure of profits always seems to lead them back to the high levels of impurities.

Infant brain damage can be caused by a deficiency of the B vitamin, folic acid. Taking estrogen, as in birth control pills, tends to deplete the body's supply of folic acid, so that if a pregnancy occurs right after stopping the pills it is more likely to lead to a miscarriage or deformity from folic acid deficiency. This vitamin, and probably other nutrients such as zinc and vitamin E, should always be packaged with birth control pills or other forms of estrogen, or at least should be recommended by the doctor who prescribes them. Animal experiments show that giving estrogen to the mother causes brain damage in the fetus. This could result from a folic acid deficiency, or from various other effects of estrogen, such as low blood sugar or high copper.

HYPERACTIVITY

The various tissues of the body can function acceptably at different levels of nutrition. For example, the skin, with its low energy requirements, seems to remain alive for several hours after the death of the body in general. The brain, with its extremely high energy requirements, is usually the first to suffer from energy deprivation. At slight levels of deprivation, the brain will simply lose functional efficiency, but more serious or prolonged deprivation can produce lingering modification, or even structural damage which is relatively permanent (and may even have transgenerational effects.[1])

Just as the skin (or muscle) has a lower energy requirement than the brain, the various parts of the brain have different requirements. The parts which are most resistant to damage are the "lowest" (or "most skin-like") and "oldest" parts of the brain, the parts we have in common with frogs. These parts regulate physiological processes, such as breathing, and so it is biologically useful that they should be

most resistant to damage. When a person is given an anesthetic, the first parts to stop functioning, or to go to sleep, seem to be just those parts that have the highest energy requirements, and which are least resistant to damage. The anesthetized person keeps breathing, for example, until very high doses of anesthetic are given, but other functions disappear one by one as the dose increases.

The front part of the brain, which is most uniquely human (and "newest") but which doesn't have "specific" function, in the usual sense, is one of the most sensitive parts of the brain. It is a very large piece of tissue, and it seems to be involved in planning and choosing, in governing the other more specific functions. (This part of the brain, as well as the cerebal cortex in general, gives us the ability to "disregard" stimuli, to use Lendon Smith's term.)

The famous Russian neuro-psychologist, A.R. Luria, has described the behavior of dogs when this tissue is damaged or removed:

> ...destruction of the frontal lobes leads, not so much to a disturbance of memory as to a disturbance of the ability to inhibit orienting reflexes to distracting stimuli...such an animal cannot perform tasks involving delayed responses under ordinary conditions, but can do so provided that irrelevant, distracting stimuli are removed (if the animal is kept in total darkness, if tranquilizers are administered, and so on).
>
> The role of the prefrontal cortex in the synthesis of systems of stimuli and the creation of a *plan of action* is manifested not only in relation to currently acting stimuli, but also in the formation of active behavior directed towards the future.[2]

Various theories of what causes hyperactivity, e.g., low blood sugar, weak radiation from fluorescent lights and TV[3] or food additives[4] and the observation that drugs which stimulate the sympathetic or adrenergic nerves (ephedrine or caffeine, e.g.) will relieve the symptoms, all are consistent with the idea that not enough energy is being supplied to permit this tissue to function properly. Low blood sugar will starve the nerves; food additives (which are usually associated with low quality foods with a high sugar content, so this theory isn't nearly so plausible as the idea that eating sugar is the main cause of low blood sugar and the associated hyperactivity) or any low level poison can serve as a stressor of nerve tissue, leading to increased energy requirements; many forms of very weak radiation[5] can lower the efficiency of metabolism, increasing its energy requirement, and brain tissue is the most sensitive tissue to at least some

kinds of radiation.

Children who are given amphetamines to keep them quiet in school don't grow as fast as they should, and remain permanently stunted even after stopping the treatment. This kind of drug can be addicting, resulting in decreased alertness when the drug is stopped. Hormonal compensation is likely to be involved, so it would seem reasonable to check at least the thyroid function in children who have been subjected to amphetamine treatment; it might help them catch up in mental and physical growth.

A recent study showed a clear association between small physical defects and hyperactivity implicating "gestational stress," e.g., hormone imbalance and malnutrition, in producing hyperactivity. These could result in either damage to the child's brain or its hormone regulation, e.g., low thyroid and high estrogen. Damaged girls tend to be too passive while boys are too active.

1. Needham, A.E., *The Growth Process in Animals,* Van Nostrand, Princeton, N.J., 1964.
2. Luria, A.R., *The Working Brain,* Basic Books, N.Y., 1973.
3. Ott, J., *Health and Light,* Devin-Adaire, Old Greenwich, Conn., 1973.
4. Feingold, B., *Why your Child is Hyperactive,* Random House, N.Y., 1975.
5. Frey, A.H., & S.R. Feld, "Avoidance by rats of illumination with low power nonionizing electromagnetic energy", *J. Compar. & Physiological Psychology 89* (2) 183-188, 1975.

FLUORIDE

Water that is naturally "fluoridated" tends to be "hard," that is, rich in calcium and magnesium. A few studies have compared dental health in areas that have hard or soft water, and have found that dental health varied with hardness of water, independently of fluoride content (Rothman, *et al, J. Pub. Health Dent. 32,* 225, 1975; T. Ockerse, *S. African Med. J. 18,* 225, 1944).

Human and animal experiments have shown that good general nutrition, including adequate protein and vitamin C and a high ratio of calcium and magnesium to phosphate, can improve dental health.

Several years ago a study was done to compare blood enzymes in a town before and after fluoridation of the water supply. Changes did occur, showing that the chemical had altered cellular metabolism.

Industrial pollution is tending to raise the fluoride content of soil and water. Foods on the average, in a study

done several years ago, contained about ten times as much fluoride as is considered desirable in the water supply. Because of the wide distribution of foods, people in low-fluoride areas will still get considerable amounts of it in their food. Burk and Yamouyannis showed an association between flouridation and cancer, but there seems to have been no discussion of this in the scientific community, other than some distorted comments by the flouridation establishments.

I think it would be more rational to help people understand the role of nutrition in health, including dental health, than to divert their attention from the real issue (our national food supply) by conducting hysterical campaigns to fluoridate the public water supplies.

"Expect poison from the standing water."

"Those that put their Bodies To endure are Fools."
William Blake

VI. DIETS

APPETITE

Low blood sugar usually causes an intense craving for something sweet. It is known that a vitamin A deficiency causes increased hunger — I suspect this acts through the mechanism of blood sugar. A deficiency of vitamin B1 causes loss of appetite. Normally, appetite is probably a good indicator of specific needs for protein, fat, carbohydrate, vitamin C, salts, and possibly other nutrients. As our tastes evolved, they had to be satisfied by whole foods, so a craving for carbohydrate wouldn't disrupt our physiology if we didn't have such easy access to highly purified (or distorted) carbohydrates.

A craving for "salt" is normally satisfied with sodium chloride (in bacon, cheese, crackers, olives. etc.), which doesn't meet the body's needs. Taking sodium as an additive suppresses the hormone which enables the body to retain sodium, and so it is physiologically addictive. In addition. the precursor hormone may accumulate, and this hormone produces inflammation (in joints, especially, as shown by the work of Hans Selye and his associates). If we could satisfy the salt craving with a balanced salt, including potassium and magnesium and calcium, we would probably be more comfortable and would avoid the salt (sodium) addiction. Low thyroid can cause loss of appetite. Thin people, even

very active people , can still be deficient in thyroid.

FASTING

The thymus gland, essential for immunity, shrinks during fasting. Chronic infections such as tuberculosis are more common in malnourished people. However, fasting has been used successfully in treating certain diseases. It can be useful in diagnosing food allergies, as in some types of schizophrenia. Its use as a weight reducing technique is probably not generally justified by the facts. A current study (1975) is investigating the possibility that a balanced salt solution will prevent the destruction of muscle and other protein-rich tissues during fasting. I have noticed that such a solution relieves feelings of stress, so I think it will prove to prevent protein-wastage.

In a study of the nature of weight loss in a two week fast, it was found that about 95% of the lost weight was from protein rich tissues (muscles and glands), rather than fat. A low calorie diet produces a slower weight loss, but in this case most of the lost weight is fat. Since fat has a very low rate of metabolism, people who lose muscle by fasting are going to have increasing difficulty in losing weight, since they will have less active tissue to consume fat. Building up muscle and lymph tissue for optimum health — even if it initially causes a slight weight gain — will make reducing easier by increasing the mass of metabolically active tissue. Progesterone is the only steroid hormone I know of which will cause the thymus to regenerate. Vitamin A spares protein, and will protect these tissues even on a fairly low protein diet (*Vits & Hormones*, 1977).

Chronic dieters can adapt to a low calorie intake (*Lancet*, April 5, 1975, Miller and Parsonage). This is probably partly from a loss of active "protein tissue." Total nutrition is needed for replacing such tissues.

Fasting and stress suppress the thyroid, and thus can aggravate many symptoms. Thyroid function isn't always restored when the fast ends.

COFFEE, TEA, AND COLAS

Coffee, cocoa, and cola are flavorings made from seeds, and tea of course is an extract made from certain leaves. This means that they must contain nutrients as well as drugs. This fact — that an extract made from plant or animal tissue contains nutrients — is very commonly overlooked. Even the companies that sell the products incorrectly describe them as containing no nutrients, except the other materials they

add to the flavoring. For example, Coca-Cola claims that phosporic acid and sugar are the only nutrients in their product, yet a standard text book indicates that Coke is rich in potassium (while Pepsi has more sodium than potassium). In a study of the thiamine content of dark roast coffee, it was found that one or two cups provide the minimum daily requirement of vitamin B1. Leaves contain magnesium, potassium, vitamins A, K, E and Q10 (ubiquinone), as well as other trace minerals and the B vitamins, so all kinds of tea must contain moderate amounts of these nutrients. About 20% of dietary niacin and manganese can be provided by coffee. In Russia, green tea is often prescribed for its vitamin P or rutin content. Seeds and leaves often contain chemicals which bind materials such as magnesium, zinc, and calcium, but these will break down and release the minerals under various conditions — the fermenting process in tea manufacture, for example, should have this effect.

Some nutritionists have noticed that caffeine is said to raise insulin levels in the blood, and from this have reasoned that, since insulin promotes the conversion of glucose to fat, caffeine must be avoided in a reducing diet. Caffeine has a reputation for raising blood pressure, but the evidence is not clear on this point: it seems to be an individual matter whether it will raise or lower blood pressure. Caffeine, in fact, is prescribed in doses equivalent to 2 to 4 cups of cofee (200 to 400 mg.) to relieve hypertensive headaches (J.P. Merrill, in *Principles of Internal Medicine*, Harrison, 2nd edition, p. 1425). Coffee improves circulation to the brain; Benjamin Franklin and Goethe are said to have used 30 to 65 cups daily. This amount would be close to the maximum safe daily dosage of caffeine, 6 grams (Bennett and Bondy, *Principles of Internal Medicine*, p. 795). Very small doses of caffeine have a "paradoxical" sedative effect, but this is a familiar effect of anything which raises the brain's energy level.

Caffeine (which doesn't necessarily have the same physiological effect as coffee) stimulates the sympathetic nervous system and raises the cellular level of cyclic AMP. Both of these effects promote lipolysis, the removal of fat from storage for use. This may account for the fact that coffee has been found to lower serum cholesterol and triglycerides, while raising the level of free fatty acids. Increased lipolysis would seem to be desirable in connection with a reducing diet. (Incidentally, estrogen *lowers* the level of cyclic AMP in most tissues.) Since both caffeine and adrenalin raise the metabolic rate, fat is presumably being consumed more rapidly. Adrenalin is known to raise blood sugar, apparently by inhibiting the utilization of glucose and increasing the utilization of fat. Coffee normally raises blood sugar, by its adrenalin-like effect. In this case, the level of

insulin doesn't seem to be the primary factor regulating carbohydrate metabolism. However, during fasting, coffee and or adrenalin might speed the depletion of the glycogen reserves and thus speed the appearance of hypoglycemia. Many of these studies seem to indicate that coffee would be a valuable part of a reducing diet, but since the results are so contrary to "common knowledge," there will have to be more experimental work done. Other factors, such as the habit of sweetening coffee, also have to be considered. An interesting study in the USSR suggests how complex these experiments can get: animals were fed either boiled water or unboiled water, and it was found that the animals receiving boiled water had significantly higher serum cholesterol levels than the animals drinking unboiled water.

Caffeine, acting through nerves as well as directly, can increase immunity. Injected into an animal's brain, it was found to slow the growth of cancer. It was recently discovered accidentally that a very small amount of caffeine mixed with the tars from cigarette smoke prevented that material from causing cancers. It was also found, in an experiment with cultured cells, that caffeine prevents the multiplication of a cancer causing virus. Caffeine stimulates the thyroid, and hypothyroidism can cause extreme susceptibility to infection. Epidemiological studies show that heavy coffee drinkers have no more heart disease (or other sickness) than non-drinkers. However black women seemed to be protected against heart attacks if they drank coffee.

Still, coffee makes many people anxious and can produce a stress-like reaction. Whether to use it or not is largely an individual matter.

NATURAL VITAMINS AND MINERALS — ANY DIFFERENCE?

Most biological molecules are produced in only one of two "mirror image" forms. Even natural (e.g., "right-handed" or "left-handed") chemicals can be degraded by harsh industrial processes into a more random mixture. The structural randomization is called racemizing. An interesting theory of aging is that racemic molecules accumulate with time; these molecules are known to have different physical and biological properties. Synthetic vitamin E may be cheap and easy to standardize, but the randomness may also be responsible for the slight toxicity of high dosages of vitamin E reported by a few doctors.

The idea that "an element" such as potassium is simply that element, without further qualification, is a strange idea to be proposed by anyone who supposedly has had a chemistry course, but that is what the American Dietetic

Association says. Elements come in different isotopes; the proportion of heavy and light isotopes of, for example, potassium, varies in the human body with age, and is measurably different from normal in cancer cells. "Natural" minerals are usually bound by special molecules, such as proteins or "pigments" (e.g., heme) and in this state do not seem to destroy vitamins, as do various water-soluble "inorganic" minerals. Chelation does not necessarily improve assimilation of a mineral — in fact it often *prevents* absorption of a nutrient, as in the case of phytic acid.

The A.D.A. officials who propagate nutritional misinformation may be honestly ignorant, or they may think it is in the public interest to lie. Either way, it is quite wrong for them to so aggressively attack the "nutritional quacks" when their own information is so dubious.

ADDITIVES AND QUALITY

An American Dietetic Association "Position Paper" on food and nutrition misinformation says "Judicious use of food additives helps insure high quality processed food." That may in some warped way be true, but it has nothing to do with the reality of food manufacturing. A reference book on additives for the food industry points out that you shouldn't *always* buy the lowest quality cheap food materials, and then attempt to give them the appearance and flavor of higher grade food by the manipulation of chemical additives, because sometimes the necessary additives are so expensive that it might occasionally be more profitable to buy a better grade of food material in the first place. This agency, when talking to the food industry, is perfectly frank in acknowledging that additives are used for the purpose of foisting inferior grades of food upon the gullible consumer. Why is the A.D.A. so intent on denying the facts? (If an apologist for the A.D.A. reads this: consider it a challenge to a public debate on the subject of your choice.)

A study was done about 30 years ago to see whether supplements given to "exceedingly well-nourished" tuberculosis patients would make a difference in their recovery. The supplement consisted of 600 milligrams of vitamin C, 75,000 to 150,000 units of vitamin A, 5000 units of vitamin D, about 4 grams of brewer's yeast, and six grams of dried liver. The control group received placebos, in "double blind" fashion. There was a distinct improvement in the group which got the supplement (see Williams' *Nutrition Against Disease*, p. 223). So many similar studies have been done it is simply unscientific to say that supplements aren't necessary when "well balanced" meals are eaten. At a symposium for pharmacists, the "professional dietitians" were arguing that

druggists should not sell any nutritional supplements without a prescription. A woman in the audience pointed out that most Americans don't take the time to prepare three "well balanced" meals every day, and that they just won't be well-nourished if they don't take some kind of supplement. The dietitian snickered "I am defeated," but went on with her plea that the druggists stop selling supplements, with the strong implication that she couldn't argue with such irrational opponents.

Individual peculiarities and stress can make it extremely difficult to stay healthy on a normal diet: however, if meals of liver, broccoli leaves and oysters and papaya can be considered normal, then supplements might generally be unnecessary.

If a person develops symptoms of hay fever, a chronic cold, asthma, diarrhea, hemorrhoids, headaches, numb fingers, dizziness, etc., it is possible that they are allergic to some of the trash which is used in the manufacture of the pills; powdered vitamins and minerals might be tried in that case, since they are more likely to be "pure" — but even these powders can contain allergens. See "Warning About Supplements." Low blood sugar, as shown by H. Laborit, will induce allergic reactions even when there was no sensitivity at a higher level of blood sugar. Since low thyroid is an important cause of low blood sugar, thyroid function should be checked (by BMR or achilles tendon reflex, even by body temperature, but not by blood tests) when there are signs of allergy.

WARNING ABOUT SUPPLEMENTS

As we age, we accumulate more and more of the heavy metals in our tissues. Lead replaces calcium, and it reaches concentrations in the bones many times higher than in the soft tissues. A bone meal supplement produced at a glue factory (where the animals were probably old) was found to contain 190 parts lead per million. The FDA has set a limit of 1½ part per million for evaporated milk, but they refused to act in the bone meal case in 1970 because they said food supplements were in a "gray area" between food and drugs; they now say they recognize health foods as food. More recently, a survey of dog food found over 5 ppm lead, again probably because of the age of the animals used. Fluoride also accumulates with age in bones. The lead in our bones is less harmful than the same amount in our soft tissues, but certain materials (chelators, including penicillamine and EDTA; bottled salad dressing often contains EDTA) are able to remove lead from bones and move it to the brain, where it

is more destructive.

Another supplement that is likely to be dangerous is "lecithin," in the form usually sold. Lecithin itself is white. When exposed to oxygen the unsaturated fatty acids oxidize, causing it to become yellow and then brown. Rancid oils are dangerous — see pages 83-84. Eggs are a good way to get fresh lecithin. Use of a choline supplement will stimulate lecithin sythesis in the body when the essential fatty acids are present. Whole foods (leaves, seeds, etc.) are less likely to have deteriorated from exposure to oxygen than are manufactured foods.

It is hard to separate cadmium from zinc, and cadmium is toxic, so zinc supplements should be used carefully Biological purification (as in oysters) is usually more effective than industrial refining.

The FDA has allowed some very strange uses of the word "natural" — in their sense, industrial processes are natural. Vitamins E, A, and sometimes D are available as natural, biological substances, but other vitamins are not. Tablets often contain paraffin and talc (which contains asbestos fibers) as the supposedly "inert" binders.

VITAMIN C: MANY EFFECTS

One of the oldest known functions of vitamin C is its role (hydroxylation) in the synthesis of collagen for connective tissue. At high concentrations, it can also depolymerize (make more soluble) the collagen, reversing one of the important features of the aging process. A recent study (J. Clin. Nutr., summer, 1974) shows that even inside the cells of membranes structural integrity is improved (electron microscopic evidence in guinea pigs) by very high doses. including the large doses suggested by Linus Pauling. Since infections have to enter through membranes, structural integrity would seem likely to improve resistance. Tyrosine metabolism, which is involved in brain function, is sensitive to vitamin C; also, vitamin C maintains tissue adrenaline levels, possibly by inhibiting its oxidation, and adrenaline is necessary for the chalones to exert their function of inhibiting cell division. (Pauling proposed a role for vitamin C in controlling cell division in cancer, but the mechanism he chose probably wasn't the correct one; there may be a variety of mechanisms, including for example the free radical processes suggested by W.F. Koch and A. Szent-Gyorgyi.) Hans Selye has demonstrated that vitamin C can prevent heavy metal (e.g., mercury) toxicity; it reduces the metal to a less toxic form, and also helps solublize and remove it. White blood cells have an extremely high affinity for vitamin C, and can't function properly without an adequate amount:

because of this great affinity, an excess of white cells, as in leukemia, apparently robs other tissues of vitamin C and produces hemorrhages and bruises.

Some people oppose the idea that nutrition can prevent or cure diseases. Many strange warnings about vitamin C have appeared in the newspapers.

INTERACTIONS

Since all nutrients work together, it's generally best to eat a variety of foods at each meal. Unrefined foods assure a fairly broad range of nutrients. People sometimes forget that meat is a "refined" food in this sense: it doesn't contain all the nutrients needed to make an animal. Nearly all Americans have porous, weakened bones and teeth by the time they are 50, because of the large amount of meat eaten in relation to other foods. When excess phosphate (from meat or wheat germ, for example) is eaten, calcium and magnesium are removed from the teeth and bones to be excreted with the phosphate. Using a large amount of milk improves the ratio of calcium to phosphorus, but doesn't supply enough magnesium to prevent tooth decay, heart trouble, and cramps. Greens and vegetables should be eaten with the animal proteins.

Eating extra amounts of liquid oil will increase your need for vitamin E, and extra carbohydrate will make you need more vitamin B1. Excess protein increases the amount of B6 needed. Some kinds of protein (cysteine rich, such as muscle and liver) also inhibit the thyroid; carbohydrate can promote the formation of T3, the most active form of thyroid hormone.

Other types of interaction haven't been very well studied, but they probably are the reason for some peculiar diet systems: allergies to one food can cause digestive problems that interfere with other foods. For example, people who are allergic to onions sometimes have a gall bladder reaction which prevents proper digestion of fats. If we added up all of the special "avoidance" diets, no one could eat anything. Many people are ruining their health by avoiding too many foods.

CEREALS, SEEDS, AND BEANS

A seed is a kind of storage device, usually containing enough material to produce a sprout and root several times bigger than the seed, just by adding water. Health food "fanatics" for many years have advocated the use of sprouted grains and beans, and used to be ridiculed by the

scientific home-economist types who "knew" that a seed contained all the nutrients that would be in the sprout. Home economists did approve of soaking beans overnight, but only because it was supposed to reduce cooking time. E. Pfeiffer used to demonstrate chromatographically how very different sprouts were from seeds in chemical composition, but it is just in the last few months that establishment (Colorado State University) food chemists have reported that sprouts contain twice as much protein as do the legumes from which they grow.

Glutin, the main protein of gluten, is a typical storage protein. Instead of the normal ratio of nitrogen to carbon, oxygen and hydrogen, glutin is extra heavily loaded with nitrogen, in the form of amide and amine groups on the side chains. When seeds are soaked or sprouted, these nitrogens combine with carbohydrates to form a large amount of new protein, consuming in the process some of the stored starch. If we eat seeds in the crude form, our digestive enzymes handle the glutin differently, producing some fairly toxic peptides (chemically related to histamine) and some ammonia; these, added to the starch, can cause gas and a variety of allergic reactions. Phosphate is also released from its storage form as phytic acid by sprouting. This reaction also produces inositol, to which the phosphate is bound. If seeds, especially legumes, are eaten without soaking, phytic acid chelates minerals such as zinc and prevents their absorption. The traditional practice of letting bread rise overnight allowed these same enzymic reactions to occur. The hasty baker is not only robbing the population of half of its cereal protein, but is also making a slightly toxic product. (Thyroid inhibitors — iodate and bromate — are added to most bakery breads.)

VINEGAR, HONEY, AND FAT

I have seen people very quickly get fat on a daily drink of cider vinegar and honey and a dose of lecithin. The folk medicine tradition behind it was probably valid — it was a good way to fatten up people who were under-weight. But somehow this got twisted into promoting it as a "reducing formula." Lecithin is a good nutrient and seems to lower the danger of a high cholesterol level in the blood. And cider vinegar and honey are both rich in necessary minerals. But the acetic acid in vinegar not only is a component of fat molecules, but it also serves to activate the process of converting glucose into fat (*Adv. Lipid Res. 9*, p. 111. 1971). Thus the formula is good as part of a weight-gaining diet, but not as part of a reducing program.

MARGARINE OR BUTTER

Animal studies show that margarine causes more circulatory disease than does butter or cholesterol. Margarine is produced from oils (which may be rancid) by the use of a nickel catalyst; a trace of nickel remaining in the oil could be harmful, but it is probably the synthetic form of fat itself which is toxic. This is another case where a synthetic chemical is entirely different, biologically and chemically, from the natural chemicals. Hardening at best would cause the oil to become like animal fats (hydrogenated), but reality is worse than theory, and hardened oil is worse than animal grease. Butter has other valuable componenets, including vitamin A, while margarine often is colored with very dubious dyes — nutritious carotene used to be used, but now synthetic mineral dyes are usually more "economical." (I don't know whether this is still true — Aug. 21, 1979.)

LIQUID OILS

E. Racker and other biochemists have pointed out that the unsaturated (liquid) fatty acids are able to uncouple the energy producing reactions from oxidation. This means that they will promote consumption of fuel without increasing fat synthesis. This is an effect similar to the "specific dynamic action" of proteins, and it is the biochemical explanation for the fact that all calories don't count the same as far as weight reduction goes. But this also means that all useful energy production is reduced in relation to heat production.

The unsaturated oils also can stimulate a dangerous kind of oxidation, in which they break down in ways that seem to accelerate the aging process. One of the more conservative investigators of vitamin E recently (in *A.J. Clin. Nutr.*, 1974) revised his opinion regarding the required amount of vitamin E: he wrote that the requirement of 15 mg./day will be increased to about 50 mg./day if the person eats much unsaturated oil (fish, seeds, etc.). People who study the amount of vitamin E needed for reproduction, and those who study its effect on the durability of red blood cells usually come up with very different figures for an optimum intake. The age of the animal or person studied is crucial: in the first year of life, the minimum dose for fertility in rats increases by 67 times. The only study of vitamin E needs in human menopause that I know of suggest that 500 mg./day is needed. Extrapolation of the rat results to humans would suggest a little bit more than that.

A study comparing Dutch babies with English babies found that the amount of unsaturated fat in the body was about 40 times higher in the Dutch babies who were fed very

little animal fat. The vitamin E requirement increases as the amount of unsaturated fat in the tissue increases.

In a big study to test the idea that liquid oil would help prevent heart disease through its effect of lowering blood cholesterol levels, the raw figures showed slightly more heart disease among the liquid fat eaters, though the difference wasn't statistically significant. There was, however, a significantly greater rate of death from cancer among the liquid fat eaters. An animal study done about 1940 suggested that this would happen: animals fed large amounts of cod liver oil nearly all died of cancer, but when they were fed the same amount of oil with a large vitamin E supplement, their cancer rate was normal. It's startling to realize that the whole group conducting the experiment failed to anticipate this result, through ignorance of the literature on animal studies of liquid oil feeding.

Some articles in medical magazines have claimed recently that an effect of diet on heart disease has been demonstrated, but they neglect to point out that the dieters also stopped smoking — and the known effects of smoking would account for the differences in heart disease.

Since unsaturated fats poison energy production, they could even contribute to heart disease. They inhibit thyroid function, and hypothyroidism is associated strongly with heart disease. In a recent study, people who ate large amounts of unsaturated oils were judged to be older in appearance than people who ate less.

Recent studies are showing that animal fats (saturated) are essential for proper brain development, and that unsaturated fats (as in typical "formulas") can damage brain development.

LAXATIVES

The daily use of a few spoonfuls of bran in the breakfast cereal, or of a carrot as a snack (or grated, as a salad), can prevent practically all constipation. A high fiber diet also lowers the risk of bowel cancer, and is being used increasingly for preventing and treating conditions such as colitis and diverticulitis. It turns out that the popular old "bland diet" without fiber was just about the worst possible thing for colitis. An extra benefit of carrot fiber, besides the bulk and moisture-holding properties, is that it captures and holds fat molecules, removing them from the body and making weight loss easier. The small amount of sugar in carrots is released slowly, so that it doesn't disturb blood sugar as much as would the same amount in a different form.

It is now known that even "purified" mineral oil contains small amounts of cancer causing chemicals. Mineral oil isn't

just a benign lubricant, it is an irritant. Years ago, autopsies of chronic users of mineral oil found that the oil had entered fat tissues, where it stayed because it can't be metabolized. When "authorities" say that mineral oil can't be absorbed by the body. I wonder what kind of a mechanism they have in mind that would keep it out while other oils are being massively absorbed.

If a person really needs a laxative, one with fewer dangers would be preferable — maybe epsom salts or aloe vera. Chronic constipation is a very common sign of hypothyroidism. Premenstrual constipation, gas and diarrhea are also associated with low progesterone.

SPECIFIC DYNAMIC ACTION

Stillman's diet book is one of the few contemporary publications to mention the fact that "specific dynamic action" of proteins leads to a variable fattening effect for a given number of calories. This is a good point in an otherwise poor book, and it is in direct contradiction to a popular establishment argument, that "a calorie is a calorie," and that weight loss is possible only by cutting calories or exercising. "Increased energy expenditure" is misleading, because the specific dynamic action of proteins (and of unsaturated fatty acids) increases energy expenditure without changing overt activity.

The idea that "a calorie is a calorie," or a simple calorie counting approach fails to recognize not only the specific dynamic action of proteins (the action of oils is usually called "uncoupling of oxidative phosphorylation"), but also fails to recognize events at the organismic level, such as insulin secretion, which form a link between the form in which food is taken (composition and timing) and the behavior, appetite, and metabolism. For example, an active brain can burn about half of all the energy consumed by the body. If brain activity is depressed, a very large percentage of the food consumed becomes available for making fat. Most physicians, who should be in the habit of considering the person as a whole, will still tell you that a "calorie is a calorie." The fact is that for many people, 100 calories of sugar is profoundly different from 100 calories of protein, even when both are taken as excess food beyond an adequate diet. The sugar will affect not only the way it is used, but it will modify the body so that the other food is not used properly.

Avoiding stimulation of the insulin-secreting beta cells in the pancreas will tend to make energy more continuously available for normal functions, including mental alertness, instead of storing it as fat. This amounts to a kind of "systemic dynamic action." Diets which take advantage of

this principle are Atkins' low carbohydrate diet, and Gordon's "Wisconsin" diet which involves frequent small meals and a fairly high protein intake. The type of protein is important, since some kinds suppress the thyroid and slow metabolism when used chronically in large amounts.

Sometimes eating more protein will increase heat production, but this can't happen unless the thyroid is working fairly well.

HCG

Many reducing clinics are using injections of the pregnancy hormone, Human Chorionic Gonadotrophin, for the purpose of making reducing diets easier and possibly improving fat distribution. This hormone shifts energy metabolism toward the use of fat rather than sugar, and so allows the blood sugar level to rise. This suppresses appetite. The hormone is produced by the placenta to make sugar available for the growing fetus. It helps the placenta to develop fully, and has been shown to have a profound influence on the development of the brain of the fetus. HCG and similar hormones produce more intellingent offspring both in animals and humans.

A suppressed or "quack" method of diagnosing for cancer has been to use a "pregnancy" test on the urine of the patient (Beard Anthrone Test), because it was believed that the same metabolic shift occurs in both cancer and pregnancy. It is now recognized by normal scientists that cancers produce *many* peptide hormones, frequently including HCG, so the pregnancy test should sometimes work as a cancer test, though it probably isn't reliable.

Recently, Dr. G.G. Costa and others at the Medical College of Virginia developed a test for cancer which probably involves this "pregnancy metabolism." They feed the patient some radioactive fat, and a person with even a very small cancer will breathe out about three times as much radioactive carbon dioxide, showing that the metabolism shifts toward fat mobilization at an early stage of cancerization.

Cancers, like embryos, live mostly on sugar. High blood sugar is maintained by causing the body to consume itself (fat and protein) while leaving sugar for the growing tissue.

HCG is very important for the health and intelligence of babies. It certainly should make reducing easier, but at present it seems risky, since it could promote the growth of a hidden cancer. Until it can be shown that this doesn't occur, I think HCG should be used only during pregnancy, when it is helpful in strengthening the placenta. Some cancers are caused to grow faster by pregnancy, and HCG might have

the same effect. However, it might also turn out to help in treating some kinds of hypoglycemia. It shouldn't be suppressed mindlessly, but neither should it be promoted mindlessly.

NOTE FOR DIETERS

While it is true that the hypothetical "well balanced meal" can provide adequate nutrition for most people, you should remember that part of that concept, "well balanced," is the assumption that the total intake will be big enough to supply the "proper" amount of calories, usually between 2,000 and 3,000 per day. The three areas in the world with the greatest life span have a normal diet of about 1200-1900 calories per day. Although standard texts still claim that 1600 calories a day is the minimum for maintaining body weight, recent studies showed that some women can't lose even on 1000 calories a day. The attitude generally has been that if a woman doesn't lose weight on 1200 calories per day she must be cheating. A "normal" diet has to be, among other things, one which doesn't produce destructive obesity. But have the advocates of the unsupplemented well balanced diet studied the proportion of the Recommended Daily Allowance in a 1200 calorie diet? Until the question has been studied properly, it isn't scientific to oppose supplements or special foods. Many Americans, especially women, deliberately restrict their food intake, so this is a question of general concern.

POPULAR REDUCING DIETS

First, the worst: Dr. Stillman's "inches off diet" is low in protein and designed to cause muscles to atrophy. This tends to make a person flabby, shapeless, and weak. By shrinking active tissue, it makes it easier to put on fat, and harder to use it up. His other diet, low in carbohydrate, is the same as Atkins'. The A.M.A. has been warning about the dangers of this "ketogenic"diet, and of course it could be dangerous to a diabetic who takes insulin and then eats no carbohydrate. But both sides of the argument were presented in *Medical Counterpoint,* and Dr. Atkins cited several dozen appropriate scientific publications to support his position. The man supporting the A.M.A.'s position found about half a dozen references to cite — one of them was a textbook documenting his quotation of the first law of thermodynamics. Maybe there is a valid reason for opposing this diet even under a doctor's supervision, but if there is, the A.M.A. hasn't demonstrated that it knows what it is. The eskimos

who used to live on meat and fat all winter seem to have proven that people can tolerate such a diet.

Many dietitians insist that you must have at least 100 grams of carbohydrate daily because the brain "uses glucose." However, the brain can adapt to using the ketones which result from fat oxidation.

Gordon's "Wisconsin" diet provides about 40 grams of carbohydrate with 90 grams of protein in a daily diet of about 1250 calories, and so is making use of the principle of low carbohydrate intake, though to a moderate degree which most doctors find acceptable — especially since there is a strict limitation on calories. The most interesting part of Gordon's diet is that the day's food is divided into at least six meals, or three meals and three snacks. This procedure is based on experiments with animals, in which the rats that learned to eat their daily ration all in one meal got fatter and fatter, while rats that ate the same amount, but could nibble on it whenever they wanted, didn't get fatter. In the wild state, this would be useful, since it would mean that when the animal found food it could store a large part of it as fat, to use later when food was scarce. But when food is always available, instead of getting fat the nibbler feels more energetic and spends the energy in activity. I have worked for a company (Medical Diet Service, in Portland and Seattle) that has kept records on thousands of people using the Wisconsin diet, and the system seems very effective. Counseling and "portion controlled" packaging of food are part of the program there, but a motivated person could get similar results, weighing their portions on a food scale and avoiding all refined carbohydrates. Getting some protein, carbohydrate and fat in each meal or snack seems desirable for many hypoglycemics, but often changes have to be made such as increasing the calories and eating more often. Diabetics sometimes use the same diet.

I have seen publicity about something called the NASA astronauts' diet, and was impressed by the large amount of refined sugar in it. One of the newspaper stories about it included a picture of a broken-down astronaut. I'm not sure what the purpose of the diet is, but I wouldn't advise a friend to eat it.

People talk about the "Mayo diet" — I think it consists of grapefruit and bacon — but the Mayo Clinic regularly denies any connection with it. I don't advise anyone to eat commercial bacon, because of the nitrite which is added to it. The nitrite combines with amino acids to make a type of chemical, the nitrosamines, which are known to be powerful cancer-inducing agents. The chemicals appear in dangerous concentrations if "preserved" meats are left at room temperature for a few hours. The smoke used in bacon, ham and

sausages is also suspected of causing cancer. And the amount of salt in bacon would probably cause retention of water (temporarily; most people adjust quickly to altered salt intake). Otherwise, the "Mayo diet" probably works for some people who can't lose weight because of their craving for carbohydrates, and are too lazy to learn a little about nutrition. It would eventually cause cramps, tooth decay and softening of the bones because of the small amount of calcium and magnesium

DIET PILLS

Amphetamines mimic the action of the "alarm" part of the nervous system (sympathetic) and so raise the level of blood sugar; this is probably the mechanism (or part of it) which suppresses appetite. Low blood sugar is associated with hyperactivity, and this is probably why the same drug is effective for the hundreds of thousands of crazy kids who get it so they will sit still in school; coffee works as well in hyperactivity, and might also help dieters. Another drink, desert tea or squaw tea (ephedra) is also effective. Coffee, unlike other stimulants, activates the thyroid gland.

However, a recent study found that in a group of 100 patients with Hodgkin's disease, 19 of them had previously used amphetamines, while only three out of 100 matched controls used them. This is apparently another effect of mimicking stress, or forcing the blood sugar up. Tonsillectomies have also been associated with an increased rate of Hodgkin's disease. Stress damages lymphoid tissue. and tonsils are composed of this tissue; Hodgkin's disease affects the same kind of tissue.

It has been found that diet pills are only temporarily effective, and when discontinued the fat returns.

FAT: IDEAS FOR GETTING OFF A PLATEAU

Fiber, such as two raw carrots per day. Coffee, as a trial, when there aren't reasons against it. Avoiding cabbages (unless cooked), mustard, radishes. Try going off estrogen treatment — usually, natural progesterone works better for controlling menopause symptoms, is less toxic, and stimulates the conversion of food to heat and energy, and use of stored fat. Vitamin A and pantothenic acid promote natural progesterone synthesis. Iodine, manganese, and cobalt are all possible problems in thyroid functioning. Related to hormones and blood sugar, get the liver healthy,

for example by eating liver at least twice a week, etc. Consider allergens, like onions, etc., that could be disturbing the liver . Sleeping less will help keep blood sugar up and fat down, unless the brain is really tired. Lower room temperature and brighter lights will stimulate the thyroid. If acne or dandruff occur, a vitamin A deficiency is suggested. Vitamin B12 and vitamin E are both needed to make use of vitamin A efficiently. Gelatin helps keep the blood sugar up, by stimulating glucagon release, and so helps control hunger. Medium chain fatty acids, found in coconut oil, are effective in turning off fat synthesis in the liver.

ONE WOMAN'S TYPICAL DIET FOR A DAY

Soon after waking, a piece of fruit. For breakfast, an egg and cereal or toast (using pre-soaked grain for the cereal or bread); milk on cereal, butter on toast. Two hours after breakfast, a snack of cheese (½ ounce) and raw carrot. For lunch, a tuna salad; fruit or milk, if more calories are needed. For supper, maybe oyster stew and a salad and a potato — or, a chicken breast, well boiled spinach or broccoli, and fruit. Just before bed, another snack of milk and fruit.

SWELLING UP (EDEMA)

Proteins are very large molecules, which don't pass very easily through the walls of blood vessels — and if they do leak out of the blood vessels into the space around cells, there are enzymes there that can dissolve them. So the blood stream maintains a high concentration of proteins, normally, which by osmosis tends to make water enter the blood from the space around the tissue cells. These proteins are largely produced by the liver. If the liver isn't functioning well, or if there is general stress, or if there isn't enough protein in the diet, these proteins tend to disappear, with the result that water accumulates outside the blood vessels. In the morning, this water will be visible as puffiness in the face, especially under the eyes, but by evening gravity will have moved it to the feet and ankles.

Not enough protein and too much sodium are the most common causes of edema. High estrogen just before menstruation often causes it. Estrogen promotes retention of sodium, which in turn helps the body to hold water. Myxedema, which results from insufficient thyroid hormone, involves leakage of proteins out of the blood vessels, and apparently a shortage of the enzymes which should dissolve them. High estrogen blocks various proteolytic enzymes, apparently including those which release thyroxine from the

colloid in the thyroid gland since it causes colloid to accumulate (colloid goiter) while reducing hormone release. It also antagonizes the actions of thyroxine on tissues. Besides eating adequate protein, it is necessary to have adequate vitamin A and zinc for efficient protein synthesis. Vitamin C and rutin (grapefruit is a good source) are needed to maintain integrity of blood vessel walls. Other nutrients are needed for normal liver functioning.

Chronic edema contributes to premature wrinkling and other signs of aging.

Members of the cabbage family (including radishes, mustard, broccoli and cauliflower) contain a chemical that interferes with thyroid function; cooking reduces this effect. Peanuts and soybeans can also interfere with thyroid function, but they act in the intestine, preventing absorption of iodine, so their effect could be overcome by eating a little extra iodine. These or similar anti-thyroid materials in various foods apparently account for the existence of goiters and cretinism in some areas where the soil contains a normal amount of iodine. The absence of other nutrients, such as cobalt, can contribute to the development of goiters.

EXERCISE

In the 1950's a national survey revealed that physical competence in the US had deteriorated, but it took J.F.Kennedy's example to make exercise popular. While jogging became popular for preventing heart disease, we were frequently told by experts how many miles a person has to run to burn off a pound of fat. However, in Russia, physiologists always remember to include the brain in their calculations, and it turns out that a walk through interesting and pleasant surroundings consumes more energy than does harder but more boring exercise. An active brain consumes a tremendous amount of fuel.

In the last century, Sechenov found that exercising one hand strengthens not only that hand, but also the other. Brain activity stimulates growth and alteration of tissues, such as the muscles. Once I decided to attend a modern dance class which began the next week. After two or three days of visualizing myself in unusual postures and movements, my muscles started feeling the way they do the day after a long hike, though I hadn't actually done any exercise. This effect of nerves on other tissues is called their trophic effect; it actually changes the chemical composition of muscle, its weight, and other properties. In the US, yoga is usually thought of either as a system of exercises, or as a strange sort of religious practice. However, at least some of the Hindu yogic traditions considered visualization to be the

point of the exercise, and recognized that the body could be powerfully influenced by mental activity. Recently psychologists have claimed that attention and visualization can cause breasts to enlarge. Even sensory nerves (such as the pain sensing nerves in the cornea of the eye) have a powerful trophic influence — so maybe it isn't just a myth about massage being useful in reducing. Bright lights also stimulate hormone production and energy metabolism, and increase muscle tone.

Many dietitians claim that exercise doesn't increase the need for protein, but the Russians have found that a combination of exercise and increased protein intake can increase the muscle mass. In a woman, this process can not only improve grace and body proportions, but it also increases the body's ability to burn up fat. Other nutrients are needed for using protein properly, and for maintaining optimum nerve functioning. However, if the exercise produces too much stress and not enough muscle action, muscles will atrophy as a result of cortisone's shifting amino acid metabolism into glucose production. Lactic acid production (getting out of breath) is the main signal of the need to produce new glucose. Therefore, "aerobic" exercise is the most stressful. Cortisone not only causes atrophy of skin, muscles and immune system, but it even has been found to accelerate aging changes in the brain.

Stress uses progesterone and can cause menstrual periods to stop. Girls who begin regular exercise (such as dancing) before puberty have later sexual development.

Exercise increases blood clotting, and so can *increase* the risk of strokes and heart attacks. Some doctors have been reporting increased incidence of flat feet, varicose veins, and prolapsed uterus among joggers. Walking is a better form of exercise.

ONE MEGAVITAMIN PROGRAM

Each person has unique nutritional requirements, and these will vary under different circumstances, but here is a program that some people use during stress. Ninety grams a day of protein, preferably including liver, eggs, milk and seafoods. Fruits and starchy vegetables can make up the rest of the calories. Calcium and magnesium, 1200 mg. each, potassium chloride 2 to 4 grams, zinc 20 to 30 mg., iodine about a fifth of a milligram, and manganese and other trace minerals from seafoods, such as kelp. Vitamin B1, 5 to 20 mg. Vitamin B2, 20 to 30 mg., Niacin, 100 to 500 mg., with the requirement sometimes increasing just before menstruation. Vitamin B6, 10 to 50 mg. Pantothenic acid, 100 to 500 mg. Folic acid. from 1 to 5 mg. Biotin, 1 mg. Vitamin B12, 25 to 100

micrograms (100 micrograms is the same as one tenth milligram). Inositol and choline, about 500 mg. each. Vitamin A, 50,000 to 100,000 units, always taken with vitamin E (200 to 400 units of d-alpha tocopherol). Rutin and the bioflavonoids are sometimes used when capillaries are abnormally fragile (some types of purpura, petechial hemorrhages, and spontaneous bruising have this cause). Vitamin D from fish liver oil, up to 2000 units a day in winter unless pregnant. The evidence for vitamin D toxicity is based on the synthetic form of the vitamin, but remember that vitamins A and D (and other oils) can be toxic in large amounts. It's interesting to compare the official propaganda about vitamin toxicity with the official silence about many of the dangers of drugs and food additives. A few major medical and pharmaceutical crimes are documented in the book *200,000,000 Guinea Pigs*. In the U.S., vitamin K is available only by prescription, but is contained in leaves. In the U.S.S.R., vitamin B15 is recognized and used, but in the U.S. it is utterly banned: the man who discovered it insulted the A.M.A. The same man also studied laetrile (l-mandelonitriles), sometimes called vitamin B17, which is suppressed as a cancer therapy, but is a common substance that is available in many seeds, such as grains and apricot seeds. There has been a great campaign of lies against this material, including stories (even on a TV doctor program) that two or three apricot seeds can be lethal.

Potassium chloride should not be used by anyone with bad kidney function, since it could accumulate, slowing or even stopping the heart. It should not be taken in tablet form, since a high local concentration stops intestinal movement, leaving the tablet in one spot where it can burn and cause ulceration. A potassium chloride powder (such as Morton's salt substitute, which is not contaminated with ammonium chloride) can be sprinkled on the food. It is best to get your potassium from foods, such as fruit.

ADAPTING TO A NEW DIET

Enzymes are continually being destroyed and synthesized in active tissues. When a vitamin binds to its enzyme, it helps to stabilize the enzyme against degradation, leading to a higher concentration of the enzyme. In the same way, the "substrate" of an enzyme (the material it changes chemically) can stabilize the enzyme. When we eat a diet that is very low in a particular nutrient, such as protein, we lose many of the enzymes involved in handling that nutrient. Without those enzymes, a meal rich in protein, for example, can liberate more ammonia than the body can dispose of, and the person can be poisoned. Many vegetarians have

experienced this "toxic" effect of meat or cheese or milk, and so believe that "animals foods" can cause mental dullness, headaches, dizziness, etc. But for a meat eater, the same process can cause vegetables to produce gas, as slow carbohydrate digestion lets bacteria break them down. Changing to any new diet, or ending a fast, should be done gradually, allowing at least several days for enzyme adaptation. The same rule would probably apply to nutritional supplements. If gas is a problem even when change of diet isn't responsible, a thyroid deficiency should be considered. Lack of stomach acid is typical in hypothyroidism, but is only one aspect of a generalized digestive depression.

ENERGY ITSELF: CrP and ATP

Although electronic energy is intimately involved in life, there are two chemicals that are involved in maintaining the "energy charge" of cells, and it is the energy charge which is most immediately related to biological function and structure. Creatine phosphate (CrP) is a kind of energy reservoir for muscle, and in a vitamin E deficiency creatine leaks out of the muscles. Aging also seems to involve defective creatine phosphate reserves (Verzar). Adenosine triphosphate (ATP) is more directly involved in all kinds of life function, for example maintaining the resting state of nerves and muscles, and governing secretion, the retention of proteins, and the elimination of toxins. ATP is more stable than many chemists realize — it is only a lack of magnesium or an excess of calcium which destabilizes its molecular structure. This seems to be involved in the sedative and anti-cramp actions of magnesium. Sensory nerves can release ATP into surrounding tissues, and this seems to be part of their "trophic" influence on healing and inflammation. A.E. Needham (*Growth Process of Animals*) has discussed the possibility that it is a "vitamin": when added to the diet of animals, it increases their growth. This must have some relevance to our nutrition, since fresh food contains abundant ATP. A day or so after an animal dies, "rigor mortis" develops because of the disappearance of ATP; a similar loss of ATP occurs in plants as they die. For many decades, fresh food enthusiasts have spoken of the "life energy" in fresh foods. Unfortunately, most scientists and health professionals still like to mystify the subject and deny that food could contain "vital energy," or that ATP could have nutritional significance.

GENERAL PRINCIPLES OF GOOD NUTRITION

1. Minimize your requirements by avoiding unnecessary stress. In Oregon in the winter, use *bright* lights, balancing incandescent bulbs with fluorescent tubes.

2. Avoid toxins. Run water 1 minute before using, and then only from the cold faucet. Do not cook tomatoes or fruit in iron or copper pans. Don't use pewter dishes. Avoid mineral oil and other solvents on skin or in air (most cosmetics contain mineral oil, and worse). Minimize contact with allergens. Be very careful with unsaturated oils, such as safflower, corn, and cod-liver oil: they destroy vitamin E and can cause cancer. The "heart diet" is a menace based on weird professional ignorance. These oils interfere with the thyroid gland.

3. Grains, legumes, and some nuts (e.g., walnuts and peanuts) are highly allergenic. Soaking or sprouting them is very desirable. Cooking cabbage, broccoli, cauliflower, mustard, etc., will destroy chemicals which poison the thyroid gland. Laetrile and PABA inhibit the thyroid. Greens and potatoes (cooked) are good to substitute for bread (especially the factory-made kinds) and for beans. Soy beans are terribly over-rated.

4. Eat frequently, using protein, fat, and carbohydrate at the same time, e.g., an egg and an orange, or a carrot with cheese. Fruit is the best source of carbohydrate; avoid uncooked starches such as nuts.

5. Use complex foods, things close to their living state: eggs, sardines, leaves, milk, etc.

6. Heat degrades protein. Canned or powdered milk has lost significant amounts of lysine, an important component of protein. The same applies to toasted cereals, nuts or beans. The heated lysine forms a carcinogen if a sugar is present, as in soybeans.

7. Any drug alters your nutritional needs. Tobacco, iron, aspirin, estrogen, tranquilizers and diuretics must be taken into account. There are special diets for special needs.

8. Don't get a "diagnosis" from anyone but a physician or other licensed person. But don't think that diagnosis is so scientific that you take an individual's opinion as the last word. For example, a girl had wasted away to 90 pounds and thought she would soon die from "pituitary atrophy," but

switching from raw foods to milk and eggs allowed her to regain her weight. Diagnoses also sometimes label a serious condition as something less serious. The appropriateness of any diet will depend on the accuracy with which your nutritional needs are known.

9. Besides their content of the essential nutrients, all natural foods contain other materials, such as hormones. There are many nutrients which are useful, without being "essential" in the narrowest sense. Under some conditions, nutrients which are not normally essential may become so. Nutrients that are synthesized by intestinal bacteria must be taken in the diet when antibiotics are used.

10. If supplements are necessary, don't use them excessively — find what is enough, but don't forget the contaminants and adulterants which may be present in pills, capsules and powders. Amino acids such as tryptophan or glutamic acid should not be used as isolated supplements.

11. A few years ago, most of the nutritional problems that I saw were caused by physicians, by refined convenience foods, and by poverty. Recently, most of the problems seem to be caused by badly designed vegetarian diets, or by acceptance of the idea that 40 grams of protein per day is sufficient. The liver and other organs deteriorate rapidly on low-protein diets. Observe the faces of the wheat-grass promoters, the millet-eaters, the "anti-mucus" dieters, and other low-protein people. Do they look old for their age?

12. Everyone should know the basic principles of nutritional physiology and have a general idea of the chemical composition of foods. Otherwise, you will be confused by conflicting claims. Become your own expert — for example, if someone tells you not to eat fruits and proteins at the same meal, get a book on digestion and absorption of food from the library, and read about interactions.

13. Examine your basic assumptions about food and life and health, and those of the experts. Is the organism a rigidly determined genetic mechanism? Is it the sum of its past environments? Does it really assimilate the environment? Is it a desire for more life? What is pleasure? Is a person a spirit temporarily trapped in a large piece of meat? Scientific questions often take on a clearer meaning when you can see their ideological context.

14. If someone who claims to be an authority belongs to a "professional organization," look at the publications of that

organization. What were they advocating 5 or 10 years ago? Are there financial motives behind their recommendations? Be suspicious, keep asking questions.

VII. THE FUTURE

HIDDEN MOTIVES

When scientific or professional publications are financed or controlled by special financial interests, we should watch for distorted reasoning, distortion by selection, and plain misstatement of facts. The Nutrition Foundation, Inc., is an important source of nutritional information in the U.S. Their trustees include officers (presidents, vice presidents, chairmen of boards, chief executives) of these companies: Coca-Cola, Royal Crown Cola, Oscar Mayer, Miles Laboratories, Hoffmann-LaRoche, Proctor & Gamble, Kellogg, Philadelphia Macaroni, Stauffer Chemical, Skinner Macaroni, Specialty Chemicals Group of ICI United States, and Dobbs-Life Savers. Can we expect their publications to be properly critical of synthetic food additives and highly refined foods?

DISESTABLISH THE PROFESSIONS

We hear a lot about the "controlled scientific studies" that supposedly have to be done before anyone can advocate something as risky as taking a nutritional supplement. The controlled nutritional studies that have been done always seem to have the wrong national origin, or have been published in "obscure journals," so that they can be ignored. I want to point out that many of these criticisms are incompetent not only because of what they ignore or suppress, but because of their double standard: if the scientific standards they demand of nutritional studies are applied to medicine, we have to say that there is no "adequate scientific basis" for many of the practices of modern medicine. Tradition is extremely important in the practice of medicine. Consider the common appendectomy or tonsillectomy. Are these practices based on animal experimentation? On human experimentation? What animal disease would be comparable to appendicitis? Would human experimentation require the sham surgery which is a standard requirement in scientific animal studies? Sham surgery would require that people in the control group with appendicitis be cut open, without removing the appendix. Since the stress of surgery can

actually affect the immune system and various physiological processes, controlled studies would not be entirely unreasonable. What other therapies have been compared with surgery in treating tonsillitis and appendicitis? If you have seen the old horror movie, "Freaks," or if you went to a circus side show in the 1940's, you can visualize the effects of an operation called a "hemicorpectomy" that was favored about 35 years ago as a treatment for a cancer of the lower part of the body — it involved removal of the lower half of the body. What kind of "controlled scientific study" was this based on? The establishment has committed itself to extremely rigorous scientific standards in its attack on nutritional therapies — and there is an extremely large body of nutritional research which meets these standards. We are therefore perfectly justified in demanding that the food, drug, and medical industries meet the same rigorous standards. (Since I wrote the above, there have been some studies of tonsillectomy and appendectomy. For example, acute appendicitis usually does not require surgery, according to the latest study.)

A PROPOSED STUDY

Many of the well publicized specialists in misinformation say that it is impossible for human beings to be deficient in vitamin E, and so we mustn't try to draw any conclusions about human sterility or miscarriages from the animal studies which showed that vitamin E is essential for implanting the embryo and maintaining pregnancy. Technically, this is known as Pig Ignorant Professionalism. The chemical processes in food don't care whether the food is consumed by rats or by people. When iron salts are added to food which contains vitamin E, the vitamin E is destroyed by the iron. When pregnant women are given pills containing up to 2000 per cent of the daily iron requirement, this iron mixes with food. The amount of money that is spent on propaganda against vitamin E could support some simple little studies to determine whether inorganic iron supplements increase the risk of miscarriage. This would seem to be a reasonable concern — is there equivalent evidence to justify the campaign against vitamin E? I don't think so.

PROTEIN AND STARVATION

At first glance, proteins seem to be required in human nutrition, in fairly large amounts. Many people are dying of what is called a protein deficiency, or a combination of protein and calorie deficiencies.

But a Russian found that atmospheric nitrogen was incorporated into body proteins by higher animals. It had been thought that only certain bacteria (such as live in the roots of legumes) could fix atmospheric nitrogen, turning it into ammonia for use in amino acids and proteins.

Then an Australian group studied New Guinea highlanders who lived on sweet potatoes and bananas, and found they excreted vastly more nitrogen than they ate, yet they remained healthy. They guessed that nitrogen fixing bacteria lived in their intestines. It turned out that E. coli, which lives in everyone's intestine, gives the chemical reaction indicating nitrogen fixation.

Then a group in Illinois (Dudka *et al., Nature 232,* 265, 1971)found that the amount of atmospheric nitrogen breathed in was not the same as the amount breathed out.

What is essential seems to be the "carbon skeleton" of the essential amino acids. If the diet supplies these along with other nutrients, then protein seems to be not so essential in the diet. If fruits and vegetables can be found which contain these substances, then the world food problem could be easily solved. Why aren't starchy, sugary and oily plants (including bananas and sweet potatoes) being surveyed to find a source of these nutrients? Since this special problem isn't "my field," I couldn't hope to get government financing for such a study. But someone should be doing it. (The protein quality of potatoes is higher, according to animal feeding experiments, than it should be, according to amino acid analysis. One of my students has demonstrated the presence of these "amino acid equivalents" in potatoes.)

REASONING ABOUT HEALTH

"What is now proved was once only imagin'd"
William Blake

The famous logician, C.S. Peirce, said that a kind of tying-together, or "colligation," of "a variety of separately observed facts" is a "generally essential step in reasoning." This process is too often excluded from formal scientific reasoning.

Tying together, forming chains of probable relationship, perceiving a cluster or constellation — these are a necessary part of any productive scientific work. In working toward a scientific goal, such a perceived constellation or pattern will direct experimentation which attempts to fill in some of the blanks in the pattern. If certain blanks remain empty, it may be necessary to re-draw the road map leading to your goal. Sometimes a person will claim to have reached a certain goal using a strange new kind of road map; if the goal is important,

it's worth seeing whether the new map is a reliable way to reach the goal. Magazines like *Prevention* are full of articles using this sort of goal-centered reasoning; there is nothing in the history of science to indicate that this isn't a valid way to proceed. However, there are some Establishment slogans that are being used in an effort to suppress any dissenting opinions in medicine and nutrition. "Raising false hopes" is one such slogan, as if being respectably sick meant abandoning all hope; but allowing the patient who stays under "proper medical care" to hope for a miracle seems perfectly acceptable.

DIETETICS OR NUTRITION?

"Always be ready to speak your mind, and a base man will avoid you."
William Blake

Dr. Andrew Weil recently mentioned that, after getting his medical education at Harvard, he doesn't recommend going to doctors. He says "preventive medicine" is a phrase everyone uses, but doctors get no training in what it means — for example, he said his training in nutrition consisted of a half hour lecture by a dietitian describing what diets were available at the hospital. Other medical schools give twice as much training in nutrition as Harvard, but even in a whole hour the doctor is likely to learn nothing more than that nutrition is a very simple matter of choosing the right menu from the list provided by a dietitian, and that "a normal balanced diet provides all the nutrients the body can use." On the basis of a 30 minute talk by a dietitian, the "Harvard educated physician" becomes an authority on nutrition (and everything else related to health, though their training has been mainly in sickness, not health), and his "professional opinion" is taken seriously by public and lawmakers.

Since a 30 minute talk by a dietitian is given such tremendous weight in our culture and laws, we should know something about their training: such awesome power, if not divine, must come from the next highest authority, but since that seems to be the AMA, this would involve a circularity.

Dietetics is often combined with home economics. It is still possible to become a dietitian without taking a single course in biochemistry. It isn't too surprising that the textbooks used in their nutrition courses contain little more than is in junior high Health texts. But it is odd that they criticize people with training in biochemistry (e.g., Linus Pauling, Adelle Davis, R.J. Williams) as not being qualified to talk about nutrition. According to a Registered Dietitian whose lecture preceded mine on a symposium for phar-

macists, physiologists aren't qualified to talk about nutrition either, and "every quack in the country is calling himself a nutritionist." A friend of mine who visited the Oregon State University nutrition department told me that a display there included books by these people (mentioned above) in a display on "nutritional quacks." Adelle Davis had a degree in dietetics and nutrition, from the University of California at Berkeley, and a masters degree in biochemistry from the USC School of Medicine. Williams, a professor of biochemistry (and the only biochemist to have been chosen as president of the American Chemical Society) has done research in nutrition for over 50 years, and is the discoverer of the B vitamin pantothenic acid, and did basic work on other B vitamins. Pauling, Nobel laureate in chemistry (as well as in peace), created much of the scientific foundation for modern medicine, physiological chemistry, and nutrition. Maybe someone is trying to glorify quackery by associating these people with the word? In judging comments about Linus Pauling, we should remember that U.S. scientists almost ostracized him when he got the Nobel Prize for peace. when war and nuclear testing were part of the respectable American Way. He was not allowed to travel abroad in the early 1950's, and this probably prevented him from getting another Nobel Prize for work with DNA. Many U.S. scientists who hated him for supporting peace now choose to call him a quack.

A study found that people with more education are more likely to eat "health foods." However, a study done by Oregon State University nutritionists found that food faddists' diets are no better than a normal diet (I don't know what they mean by normal; the US Department of Agriculture found that close to half of the US population has a nutritional deficiency, so normal is bad). The dietitian reporting the study on TV said that faddists avoid many of the good foods like white bread, and that we should follow a normal diet to "eat all the food God gave us."

NUTRITION AND CONSCIOUSNESS

"Worldly revolt of the individual comes from an interior revolt that has sought out health and natural physical processes subtle and gross."

Michael McClure

"...the conscious subject has for his object the infinity of his own nature."
"One is what he eats."

Ludwig Feuerback

"One food (agricultural) scientist is worth more than all the economists in the world."

Karl Marx

There are attitudes, ideologies, and institutions which hate anything that threatens to be useful. Effective knowledge is likely to upset everything that's neatly formalized, including the livelihood of the middle class. Commenting on the hostility of Freudian psychiatrists toward nutritional therapy for neuroses, Aldous Huxley said "poor fellows; what will become of them?" The anthropologist M. Harris says "Sometimes I think that the primary function of establishment anthropology is to fog the truth...It stays away from questions about the causes of war, the causes of sexism, the causes of racism. It stays away from all statements of causality...Academics are the high priests of the inward-turning consciousness that has spread through America."

Nutritional knowledge threatens to be useful. Biochemically trained people like Linus Pauling, Roger Williams, Adelle Davis and Abram Hoffer who write about nutrition are called "quacks" by establishment dietitians who may be trained in home economics, and who may not understand, for example, how an iron pill might cause anemia.

Mystification of food takes many forms. I remember seeing in Mexico a horribly poor (i.e. probable daily income less than 20 US cents) woman feeding her baby Pepsi Cola and pieces of a white wheat roll. Those things are heavily advertised in Mexico, and even to people who can't read they represent "class." The institution of eating three meals a day and dessert after supper is a mystification of food. Trimming the fat off your meat and avoiding pork to "keep your cholesterol down" is a multiple mystification.

Honest ignorance exists, but there is also deliberate falsification: consider the claim that additives are used so that we can have high quality food. A publication intended for industrial food chemists tells the story more bluntly, warning the manufacturer that it isn't *always* the best policy to buy the lowest grade of food and then make it palatable with additives, because sometimes the adulterants cost more than is saved. In other words, profit is the only important factor, and sometimes, conceivably, it *might* be profitable to sell good food.

When you start looking for ulterior motives, you might conclude that your physician is greedy, that your chemistry professor has a contract with the rubber company that makes ice cream, and that food producers are so pleased with their profits that they don't care about the increasing numbers of deformed and mentally retarded babies, or the increasing rate of cancer and diabetes. If you do this, then

you are probaby involved in a demystification of the world. Eating good food can alter your consciousness; so can thinking about how we're going to get it.

ABOUT FEELINGS

About 1959, I realized that feelings of love and anxiety had particular forms and locations in the front of the body. Gradually, I learned that these could be modified intentionally, and that social feelings and senses of personality and place consisted of "conformations" of these plexuses. Even in brief social encounters (of a few seconds), these body feelings may take on a conformation of openness and love, of sexual feeling, or of a closed anxious coldness. In the pleasant experience, the visceral feeling resembles channels which open and extend outward toward the other person; at times, these channels seem to make powerful contact with the other person's. Occasionally, when I feel very energetic, especially on sunny days, I have an intense sensation of sweetness that seems to travel up from behind and below my navel, to a spot behind my sternum. I call this my body's smile energy, because it feels the same as the pleasure which goes with a smile.

When I described these perceptions to an older person, she reported having lost those feelings in middle age, and she said it seemed that they had been "insulated" by the extra fat she had put on. (People who don't notice those sensations may wonder how a person could feel insulated from something which is inside oneself. The point is that they are sensations of openness of the body to the world.) Her comments caused me to associate the feelings with thyroid function and metabolic rate. I have noticed that when I feel sluggish from bad weather or diet, those feelings seem muffled, or barely perceptible.

Recently, I described these body feelings to a friend (in her early twenties) who wasn't sure what I meant. For several weeks, she didn't experience anything that seemed like my descriptions. She began taking thyroid a few weeks ago. Within a few days of the time that she had increased her dosage (from ½ to 1 grain), she told me that she had begun to feel things she had never felt before, feelings of openness and intensity in her body. Another friend, the same age, said she had orgasms easily when she was 18 and 19, but in the last 2 or 3 years had been unable to. She claimed to have no emotional feelings in her body, even when she desires, except for vibration when she is sexually excited, and an awareness of something in her pelvis. When I mentioned the association between thyroid and nerve reflexes, she recalled that she had been put on a large dose of thyroid hormone in

her late teens, just about the time she discovered she could have orgasms. Moving to Oregon, her new doctor had taken her entirely off thyroid. She stopped having orgasms, and begin to have frequent suicidal depressions. A little thyroid stopped her depressions, without increasing her pulse, which was only 60. She consistently increased her use of thyroid, and has since reported having orgasms.

Athletic training is known to slow the pulse. Cortisone, produced by stress, inhibits the thyroid gland. (When the thyroid is low, less oxygen is needed, so this is a useful adaptation for increasing endurance.) These hormonal changes are now known to produce sterility in both men and women. Estrogen, used for birth control, also elevates cortisone and interferes with thyroxine. Estrogen, like a thyroid deficiency, can lower sexual responsiveness. My guess is that heavy exercise, such as running, will lower sexual responsiveness as it lowers fertility. Emotional stress, by causing the same hormonal changes, would have the same effects. Nutritional deficiencies and environmental toxins, by causing stress and hormone imbalance, could do the same.

If someone has never experienced a full sexual response, it is meaningless to ask about the occurrence of "orgasms." Ease or difficulty in responding sexually, though, and perceptions of bodily emotions, might serve as a subtle indicator of hormone balance, especially thyroid sufficiency.

DESIRE, THE LIBERATOR OF SEXUAL OBJECTS

Men, out of touch with their energies and natural desires and dreams, have kept women in chains. Passive and weak, women have kept to themselves the wholeness and richness of their experience.

Reasoning and competing men have believed that they possessed women, but the centered and prolific human female world was overlooked by the greedy devouring male, who took part of her existence and believed he had taken it all.

Wishing to be liberated, no longer passive and weak, many women are becoming reasoning competitors, but in doing so are losing contact with their bodily energies, desires, and dreams.

It is obviously hard to desire the kind of man who has produced, and been produced by, western civilization. He is the competitive athlete or the competitive sedentary business-man, or the competitive intellectual rationalizing his superiority over all beings.

Sexual desire has been so closely involved with enslavement, many women feel very concretely that desire

must be overcome if they are to gain full human status.

Being a sexual object has meant being enslaved and diminished.

Gaining the social, economic, cultural, intellectual, and sexual rights of men will not liberate anyone, because these rights and roles are where the ugliness of maleness is. It is not the penis that is fascistic, domineering, exploitive, corrupting. The penis is the male animal-flower, a soft-firm dildo, a warm dream.

All objects are desirable, no object enslaves; imposed systems enslave.

If we see that to be an animal, to be human, is to desire, then we see that to be understood is to be understood as desire. If our perception is purified, there is no mere object.

In a society which considers a corporation to be a person, we have to be careful when we ask to be treated as "a person, not an object." The society's definition of a person is something like "an emptiness with rights." We want equal rights, but we also want equal fullness. To achieve that human fullness, men have to be freed from their abstract reasoning aggressive possessiveness, and women have to be freed from their passivity.

Intersubjectivity is possible when we recognize a mutual desire for growth. This kind of contact expands our self and our known world, while allowing the other to expand.

Men relate by looking at the world together. Men and women relate by seeing each other as perspectives on the world. A sexual subjectivity, rather than a sexual object. Intense relationships between women are just beginning to be explored. Intense relationships between men and women should be further explored — new selves will be evolved, and new methods for exploring will be discovered. But before this is possible for everyone, the whole system of capitalist imperialism has to be changed, so that being human is not defined primarily as having an economic role.

Men and women have real differences, but the nature of these differences still has to be investigated, in the course of mutually supported growth.

FERTILE PAIRING

The sexual pair is the unit of invention.

It's as though the brain of each were incomplete. Undoubtedly culture exaggerates some biological differences, but it seems to erect barriers to the kind of interaction that leads to dreaming discovery. Change and adventure are important for our energy system, and the present authoritarian culture is opposed to fundamental change.

In terms of hemispheric balance, girls depart less radically from bilateral symmetry, and reach a mature stability somewhat earlier. This is consistent with their characteristic "global" consciousness, as opposed to the male's analytic style; culture is definitely a factor in shaping these styles, but the larger brain/body weight ratio of the female is likely to be involved — that is, more brain would tend to achieve better balance.

At first, this feminine brain superiority, if we generalize from the general mammalian meaning of the brain/body weight ration, seems to be a put-down of men. However, the view I am proposing attributes some virtue to the masculine imbalance itself.

When I noticed a similarity of feeling between excited, dreaming, tottering mental exploration and the plain hungry low blood-sugar state, I realized that a certain kind of alertness is like a falling away from old habits.

In this view, masculine consciousness would be characterized as impatiently stumbling along into new territory, while the female provides the understanding necessary for steering an intelligent course.

More creative individuals of either sex probably experience both of these tendencies, cyclically, to a greater degree than does an individual who remains deeply imbedded in the culture, but real mental intercourse of the sexes seems to offer the greatest support for creativity.

from "EVOLUTION AS HUMAN SCULPTURE," 1967

. . . we can begin to think of ourselves, our bodies, as objects, without the old perverse connotations of "possession," "non-living," "passive-mechanical." We can recognize that in changing our viewpoints, we are changing our bodies in real structural ways, and that in spite of the magical nature of our functioning, there are real bodily inertias that we have to work with.

Wanting to complexify our body structures, so that the inertias will interfere as little as possible with the activity of our consciousness, we will use a sort of "material dialectic." When everything seems to be perfectly under control, and is going smoothly, and not much is being learned, it means that we are structurally complex enough for the demands of the situation, and that below the surface of experience there are inertia structures that are slowing our multiplication of viewpoints.

This means that to evolve, and to expand our consciousness, it's time to look for the most improbable, the most demanding, confusing, even threatening, situation. The feeling of adventure that directs the choice of activities is the

same as that of a sculptor, thinking and imposing intentions as far as possible, but finding new intentions and new problems in the act of physically attacking the stone with the hands and arms, and in the constant discovery of essential and accidental properties of the stone. We have to believe that there is something really new and important to be discovered.

The redundant torpor of jazz, and the patterned gestures of most dancing are the opposite of adventure, and these things assert that past and present are sufficient, that pleasures are not formative.

The sculptural feeling for the massiveness and resistance of your own body in confronting reality is involved in the sexual process, which is another dimension of evolution. For the active consciousness, perception is emotion; desire is inherent in the perception of a mate, and perception of self is part of the perception of other. For the old consciousness, therefore, desirable characteristics were generally not related to evolutionary values, since the self had only the dimmest awareness of such values. A woman's need for security, in a society which makes women dependent, will cause her to be attracted by wealth and power, without reference to her subtler needs.

Experience is stored in our tissues, and is passed on, but not as Darwinian "gemmules." What is stored is flexibility, potential, and energy capacity. The mate who can challenge by complementary perceptions arouses deep energetic processes, felt as desire, and as knowledge projecting itself into the future. The hormonal and probably electrical changes, the subtle structural changes that appear as increased stickiness, hysteresis, are part of the individual's organismic development, but they are also at the heart of evolution of the species. Great loves make great people. By recognizing, knowing, responding to, more of the other, we evolve the organ of response, the brain.

If this stuff is true, then reproduction should be delayed until there is maximum capacity for response, and a maximum of personal ripeness, to elicit such intense and general responses from a mate.

APPENDIX

SOME DEFINITIONS

Carbohydrate: a molecule containing carbon, oxygen, and hydrogen, e.g., sugars and starches. The formula is, roughly, any multipe of HCOH.

Collagen and connective tissue: one of the best known "pure" proteins, gelatin, is made by boiling animal skin or other tough tissue to extract collagen ("glue source") which is the main protein component of animals. It forms a tough jelly in which cells are embedded. Other macromolecules, especially hyaluronic acid and chondroitin sulfate, are major components of other extra-cellular materials, such as joint fluid, eye jelly, cartilage, tendons, etc. Gelatin lacks essential amino acids (cysteine, tryptophan) and so nutritionally will not serve as a protein source for general use.

Dietetics: (see Nutrition).

Glycolysis: the degradation of glucose (or glycogen) to pyruvic acid, with the production of a small amount of energy (ATP), relative to the very efficient oxidative production of ATP which consumes pyruvic (or lactic) acid, or fat (or acetic acid) or carbohydrates derived from amino acids. Alcohol not only is oxidized as a "fat," but it apparently inhibits the wasteful conversion of protein to fuel and so allows protein to be used more efficiently. The wasteful glycolysis of cancer can sometimes be controlled by such "physiological" means.

Lipids or fats: molecules containing mainly carbon and hydrogen, though biological fats typically have a carbon-oxygen-oxygen group at the end, which increases their solubility in water. These relatively soluble fats are the fatty acids, which can combine with glycerin to form triglycerides (three fats, one glycerin). We synthesize many fats, but some others must be included in the diet — essential fatty acids, or "vitamin F."

Lipolysis: the breaking down of fats, it commonly refers to the breakdown of storage triglycerides into fatty acids and glycerol.

Minerals: generally, these are all the elements that are needed by organisms, but which can be found in nature independently, though carbon, nitrogen, and water are not

called minerals. They have structural, chemical, and catalytic functions.

Mitochondria: small "compartments" in the cytoplasm (the viscous part of the cell, everything but the nucleus), they are responsible for much of the cell's energy production (as ATP) and oxygen consumption.

Nutrition: a branch of biology or physiology, an area of scientific study which overlaps many other areas, including biochemistry, physiological chemistry, reproduction and growth, microbiology, general and comparative physiology, etc. Easily distinguished from dietetics, which tends to be concerned more narrowly with the regulation of food intake, but also with cooking and food prices, serving food, and professionalism.

Proteins: with water, proteins are the main structural components of the animal body. They are also the catalysts (enzymes) which govern the rate of almost every chemical reaction in the organism. The third type of protein is used for immunity: antibodies. Proteins are synthesized in cells in a linear manner, connecting many (50 to a few hundred) amino acids in a row, but the most soluble (hydrophilic, water-loving) normally take on a compact, roughly spherical form. They are classed as "macromolecules," molecules which are so large that they have special properties; it is sometimes more useful to think of them as a "system" than as a unit. When proteins are digested, they are broken down (more or less completely) into amino acids. These smaller molecules (a little smaller than sugar molecules, they weigh roughly 100 times more than a hydrogen atom) are composed of carbon, hydrogen, oxygen, nitrogen, and sometimes sulfur. Along the "backbone" of a protein, the atoms nitrogen, carbon, and another carbon, from each amino acid, repeat regularly: N-C-C, -N-C-C, -N-C-C, etc. The basic amine (ammonia-like) nitrogen at one end combines with the acidic carbon at the other end, and a variety of other atoms are attached to the middle carbon, as a "side-chain." The nature of the side chain is most important in determining the function of the protein. If the nitrogen is removed from the amino acid, what remains is a small acidic molecule, which in some cases is a common "fuel" molecule. Eight (roughly) of the 22 amino acids have a "carbon skeleton" which we can't synthesize, so they must be included in the diet — as protein, amino acid, or possibly as "skeleton."

Starch: a "macromolecule" consisting of strings of sugar molecules. They may be used for storage or for structural purposes, as in connective tissues. Glycogen is the storage

starch of animals.

Sugar: a small carbohydrate, usually from 3 to 12 carbon atoms. An alcohol is intermediate between sugar and fat, usually with one or two oxygens per molecule.

Vitamins: any chemical which is necessary for life and has to be obtained in the diet, in small amounts — i.e., specific substances other than fuel molecules, protein (or amino acids) or minerals. The category includes, roughly, everything that's essential that doesn't fit another category. There is a popular tendency to give them the neat definition of "co-enzymes," that is, a catalytic group other than a mineral which is associated with a protein to form a functional enzyme, and which can't be synthesized by the body — but unfortunately for that definition, some vitamins seem to have functions other than as co-enzymes. This mistaken definition often leads to the reasoning: "There are only so many molecules of each enzyme; therefore a similar number of vitamin molecules is the maximum that can be used." First, the number of enzyme molecules is variable; second, several factors can influence the association of co-enzyme with (apo)enzyme, so that there may be no effective "binding" until the protein is surrounded by a cloud of vitamin molecules; and third, the vitamin's function may not involve an enzyme at all. The "vitamin equals co-enzyme" concept seems to result from "quicky" biochemistry courses, combined with no study of nutrition.

UNITS

The labels on vitamin bottles can be misleading to people who don't realize that a milligram (mg.) is 1000 times bigger than a microgram (mcg.). Usually the only vitamins that should be listed in microgram amounts are B12, biotin, and folic acid. For example, 50 mcg. of pantothenic acid is too small to do any good; it would be about the right dose for a big bug, but I have seen it on many vitamin labels. Apparently these are easy units to confuse — in one of my nutrition classes, a woman who had been a nurse for 30 years said she had always thought a microgram was bigger than a milligram.

The next larger common unit, the gram is easier to visualize: roughly a quarter of a teaspoonful, or about 1/28 of an ounce. One milligram is a thousandth of a gram. Sometimes the English unit, grain, is confused with the gram; a grain is abbreviated gr. (gram is g.) and is only about 65 milligrams.

Calories (or kilocalories) are the chemical energy of food expressed as heat, and for many foods the figures given in tables are misleading. For example, many vegetables contain carbohydrates with a variable digestibleness: storage or cooking can modify the amount that is available, and different people will absorb different proportions of them. The calorie values for fats (over 9 calories per gram) and carbohydrates (about 4 calories per gram) are more consistent. Chemically, protein has about 5 calories per gram, but this figure isn't very meaningful biologically. Taking "calories" out of context can give bad results — some people avoid carrots as being "high in calories," but carrots can be very effective for losing weight, partly because their high fiber content binds a large amount of fat and carries it out of the body.

"International units" are used for vitamins A, D, and E. The minimum requirements for these vitamins are, in weight, close to those for vitamins B1, B12, and pantothenic acid, respectively. In international units, the figures are 5000 to 8000, about 400, and 25 to 30, but these requirements are known to vary with factors such as the amount of sunshine, the season, and other nutrients in the diet.

Vitamin A may also be expressed in the new unit, RE (retinol equivalent), which is 5 times as large as an IU.

NUTRIENTS: PLANT SOURCES; PLACES CONCENTRATED IN ANIMALS; FUNCTIONS

Vitamin A: leaves, carrots; eye, liver, skin; light sensitivity, protein synthesis, cell division regulation.
Vitamin K: leaves; liver; clotting, energy.
Vitamin D: milk products; teeth, bones, nerves, muscles, clotting — mineral metabolism.
Vitamin E: leaves, seeds; liver, fat, brain; energy, clot removal, cell integrity.
Vitamin B1: nuts, leaves, bran; liver, cornea; oxidative energy metabolism.
Niacin: nuts, seeds; liver; energy, synthesis.
Vitamin B6: leaves, fruit; meat in general; synthesis, especially proteins and nerve chemicals.
Biotin: seeds, leaves; liver, oviduct; synthesis of fats and oils, carbon dioxide metabolism. ,
Inositol: fruit, seeds, leaves; liver; mobilizing fats, stabilizing molecules and cells.
Vitamin B12: possibly in leaves, such as comfrey; pituitary gland, liver, other animal tissue; blood formation, nerve function, and it has been suggested for irregular menstruation and abnormal vaginal discharge.
Pantothenic acid: fruit, seeds; liver, glands; hormone

production, energy, synthesis.
Folic acid: leaves, nuts; liver; synthesis. especially nerve, blood, immune system.
Vitamin C: fruits; glands: connective tissue, immunity, detoxification, anti-cholesterol.
Potassium: all solid parts; intracellular: lost in stress, deficiency mimics diabetes.
Sodium: saps especiaily: extracellular: well retained, except when adrenals are damaged or it is taken in excess.
Magnesium: leaves, molasses; intracellular: enzyme control, stabilizes nerves, muscles, etc. activates immune system, helps regulate sugar metabolism.
Calcium: milk, leaves; mainly extracellular: enzyme and permeability control, muscle contraction, clotting.
Phosphorous: seeds, yeast: meat, milk, intracellular: growth, energy, etc.
Iron: bran, molasses: blood, meat: respiration. enzymes.
Iodine: kelp, sea plants; all seafoods, thyroid gland; growth, fertility, nerve function, oxidation.
Copper: soy beans; liver; mitochondrial oxidation, elastin production in arteries, skin, etc., possible regulatory function in hormone cycles.
Zinc: sea plants: oysters, thymus gland; immunity, wound healing, fertility, nerves.
Ubiquinone: leaves; liver, all tissues; energy production, muscle action, acts with vitamin E.
Fiber: Carrot fibers are best for intestinal stimulation and binding of fats; leaves and bran contain fiber that is slightly less effective, though the other nutrients in them are very valuable.
Essential fatty acids: seeds, leaves; liver, pork, chicken; can prevent eczema; used in lecithin synthesis, and probably in prostaglindin hormones; kidney function.

HOLISTIC PHYSIOLOGY: A DIAGRAM

The wavy line across the middle of the picture represents the "internal environment," the fluid that bathes all our cells, which is kept as close as possible to an optimum composition. Water, salts, acid-alkali balance, hormones, sugars and other nutrients are all regulated as smoothly as possible. An abnormal environment can disturb the balance of one substance, and if the organism can't replace it from the environment or tissue stores. complex adjustment of many components can restore a reasonable balance. But the greater the demand, the smaller will be the reserve capacity for a future adaptation. Therefore, part of our "physiology" is the adjustment of our environment so that it more closely suits our needs. If our environment fails us a little today, our

needs will be much greater tomorrow. For example, experiments show that if the cells of the cornea (eye surface) become deficient in vitamin B2, they can no longer pick up that vitamin from the body fluids when the animal is fed a normal amount of the vitamin. An extremely high dose must be given before the tissue can regain its normal amount of the vitamin. A similar effect has been observed with niacin, and it probably represents a general property of living material (physical systems show a similar effect, called hysteresis).

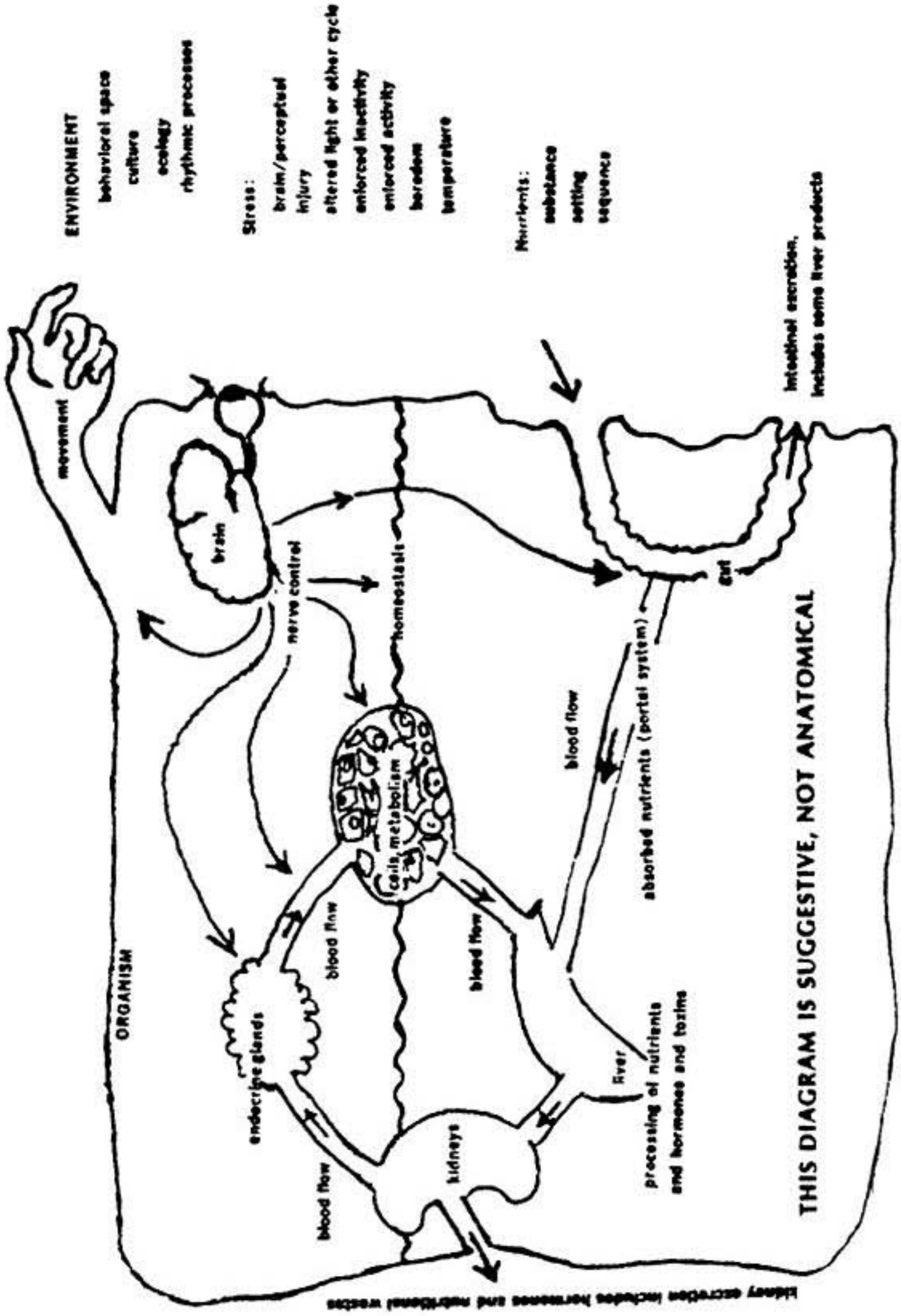
This kind of effect, this "residue" from past environments, has to be considered in deciding what a person's nutritional requirements are. Memory and intention must be considered as part of physiology: evaluating the quality of support from the environment requires a long time scale, even "transgenerational." Transgenerational effects are typically ignored or denied by establishment "science": A.E. Needham in *The Growth Process in Animals*, reviews some of the older studies of nutritional effects extending beyond a single lifetime. More recently, Zamenhoff and others have shown transgenerational nutritional effects on the brain. Absolutist genetic theory — plus bad reasoning — serves to justify a given level of disease in the population. For example, nutritional standards are determined with reference to the present level of health in the nation, because this is seen as being determined by factors other than nutrition. The national health has deteriorated in many ways over the last 30 or 40 years, and the average diet has changed. Official national nutritional standards have been revised downward over this period.

Emphasizing the uniqueness of individual needs should be seen in the context of looking for the most general principles; this can help us to perceive meaningful configurations, making otherwise trivial things significant. I think a biophysical approach to the cytoplasm is one of the "principles" that will help in perceiving patterns. Other more specific and immediately useful ideas include stress, the use of sugar efficiently or wastefully, and the energy charge of cells. These are explained in other sections.

A NOTE ON REFERENCES

At present, Nutrition for Women contains more than 80 references to the scientific or medical literature. Since it is compactly written, almost every sentence is based on at least one publication. Complete citations would therefore require a bibliography at least as long as the present text, meaning that the book would cost more than twice as much. Often I

have used older sources, when their results have stood up well, because I want to emphasize the cultural lag which exists between discovery and professional awareness and application. Unfortunately, some professional half-wits who have never read a scientific paper are able to point at the date of citation and say, "well, *now* we know better than this." This happens frequently in relation to the information on estrogen and iron, especially, even though many studies have appeared in recent months confirming the older data. The only real solution to this problem is to change our system of education and information distribution. However, if more detailed citations are needed for a particular problem I will be glad to provide them.



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CHRONIC FATIGUE

Various researchers have found that the cells of fat, or depressed, or tired people are in a low energy state, and, increasingly, it is being recognized that this low energy state resembles hypothyroidism. Many things can cause hypothyroidism--too much estrogen or cortisol, too little progesterone, a diet containing too little good quality protein, too few calories, or diets containing significant quantities of beans, lentils, or undercooked broccoli or cauliflower--but in our culture unsaturated oils are probably the most important cause.

As early as 1951, it was known (Kunkel and Williams, J. Biol. Chem.) that the polyunsaturated fatty acids strongly inhibit the crucial respiratory enzyme, cytochrome oxidase, and that inhibition of this enzyme has a very important effect on the whole animal, suppressing its metabolic rate, reducing the number of calories it can burn. It is now known that polyunsaturated fats interfere with thyroid hormone in just about every conceivable way.

One of the most common symptoms of hypothyroidism is lethargy, fatigue that persists even while getting extra rest and sleep. Everything is inefficient in hypothyroidism, even sleep. Occasionally, a low thyroid person can compensate for the basic metabolic defect by producing very large amounts of adrenalin. These people seem to have excess energy, and sometimes need less sleep than average, but on the level of tissue function, they are similar to the chronically fatigued people, being slow to produce energy. Compensating for low thyroid with high adrenalin creates specific metabolic problems, including circulatory and heart disease. Slow relaxation of muscles, caused by respiratory inhibition, can produce chronic soreness and stiffness, which is a common feature of the "chronic fatigue syndrome."

Cold fingers and toes are one of the most common signs of hypothyroidism, and result from a low rate of metabolic heat production, combined with the effects of adrenalin, restricting blood flow to the extremities to preserve the body's limited heat. Experimenters have found that sodium tends to increase body temperature, and eating additional salt sometimes helps to break out of the low energy hypothyroid state; one effect of extra salt is that it makes it easier for the body to retain its magnesium, which is very closely associated with cellular energy.

All animals respond to the stressful effects of reduced sunshine in winter with adjustments in their thyroid functions. Typically, mammals need several times as much thyroid during the winter as they do in the summer. If a person is taking a balanced thyroid supplement, increasing the dose is often all it takes to avoid the lethargy, weight gain, and "seasonal affective disorder" that often occurs in the winter. A variety of stress-related diseases tend to get worse during the winter, and sometimes they make their first appearance in the winter. The rate of aging is greatest in the winter, and the risk of death is highest. All of the protective hormones tend to fall during the winter.

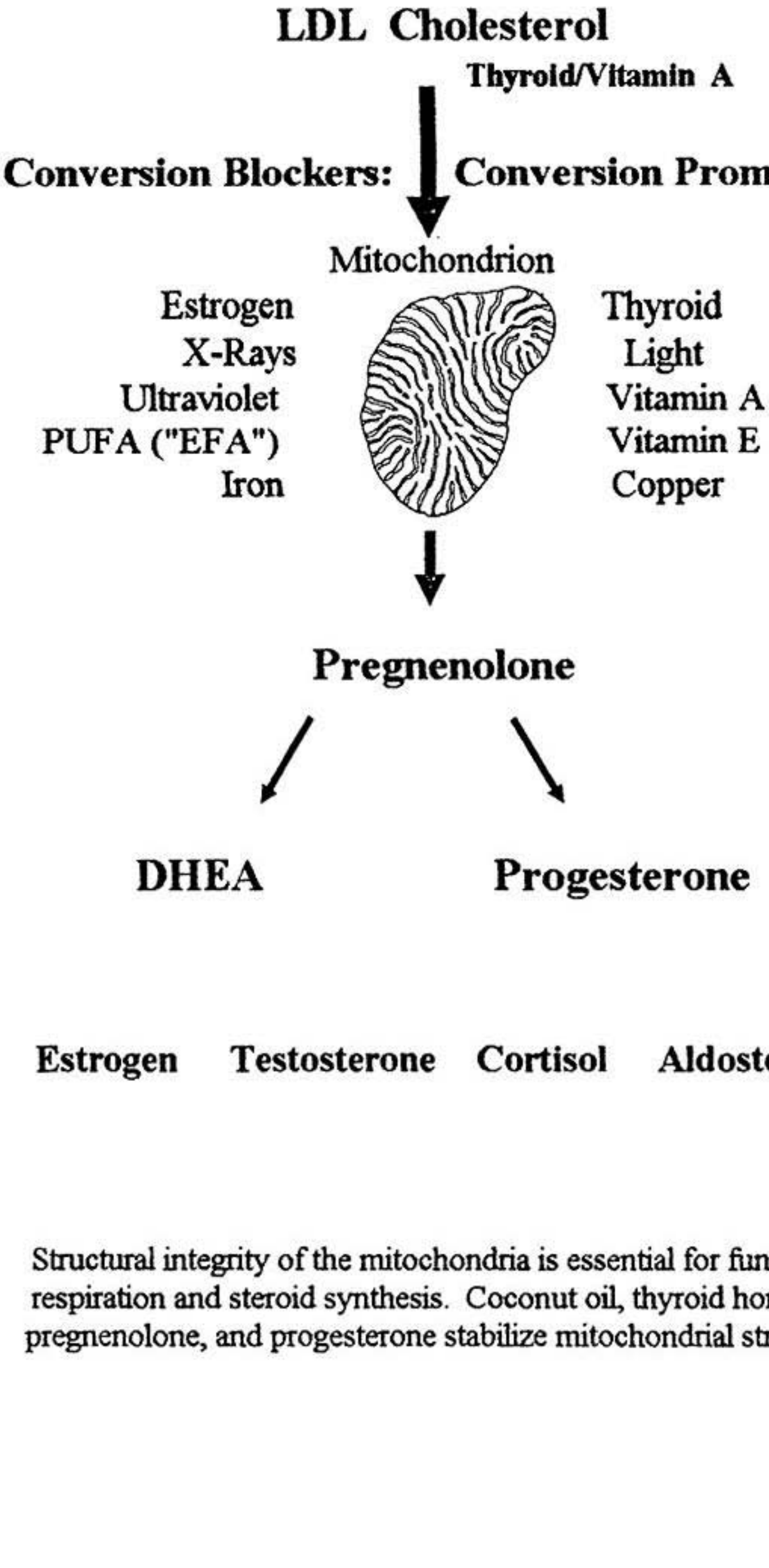
On pages 119 and 120, I have added two new charts that schematically show the relation of thyroid hormones and other factors to the protective and youth-associated steroid hormones.

PREGNENOLONE

Pregnenolone is the first steroid produced from cholesterol, under the influence of thyroid and vitamin A. Large amounts are produced in the brain, by certain glial cells that are one of our essential anti-stress systems. The need for producing pregnenolone is associated with a

sense of being under stress, and taking a supplement of pregnenolone causes many fatigued, stressed people to have a renewed sense of ability to meet challenges. Ordinarily, thyroid hormone supplementation has the same effect by promoting the conversion of cholesterol to pregnenolone, but when there isn't enough cholesterol, or when the mitochondria have accumulated damage (such as might be produced by tissue accumulation of iron, displacing copper), pregnenolone itself seems to be needed. For many years, I have felt that the skin might be one of our most important endocrine organs, and it has been demonstrated that it is able metabolize various steroids. I suspect that pregnenolone is as important to the skin as it is to the brain. Several years ago, I noticed that my facial skin, that had gradually seemed to loosen with aging, suddenly contracted back to a snugger, more elastic fit shortly after I started taking a small amount of pregnenolone. Since then, I have seen the same thing happen in other people; one man said it was like an over-night face lift, when he took a large amount, that also had a profound effect on his mood. A few years ago, the fiber cells, which are a major component of the skin, were found to contain the same contractile materials that muscles have. I think pregnenolone allows these cells to contract, restoring firmness to slack skin. Pregnenolone can quickly cause other very rapid "anatomical" changes, though, that seem to have more to do with eliminating edema, than with contraction of cells, such as causing protruding eyes (in Graves' disease) to recede, or causing joint cartilage to function normally and painlessly, or causing lungs to oxygenate the blood efficiently in people with emphysema. The charts on the following pages show some of the factors involved in the formation of pregnenolone.

Factors in Steroid Synthesis



Structural integrity of the mitochondria is essential for functional respiration and steroid synthesis. Coconut oil, thyroid hormone, pregnenolone, and progesterone stabilize mitochondrial structure.

ISOPRENE (Precursor, shows up in nocturnal breath, probably indicating interference with its use.)
CHOLESTEROL (Vitamin A, thyroid, and mitochondrial integrity, which depend on factors that limit lipid peroxidation, are needed for its conversion into pregnenolone.)
PREGNENOLONE (Formed in mitochondria, probably exits from that structure by a solubility gradient as well as specific mechanisms, to the cytoplasm, where tissue-specific enzymes in microsomes oxidize it further to either:)
DHEA or PROGESTERONE (These and pregnenolone should be abundant, probably saturating cells to the solubility limit.)
ESTROGEN, TESTOSTERONE, CORTISOL, AND ALDOSTERONE (These are the "terminal" steroids, which vary greatly according to circumstances; in excess they are toxic, and in the absence of saturating amounts of the precursor steroids--which are slightly antagonistic "buffers"--even normal amounts can have exaggerated effects.)

The accumulation of cholesterol clearly indicates the failure to convert it to steroids, so elevated cholesterol is a fairly reliable diagnostic indicator of hypothyroidism. The appearance of isoprene in some people's breath during the night is probably an indicator of something interfering with the synthesis of cholesterol. Highly allergic people often have extremely low cholesterol, making it impossible for them to synthesis normal amounts of the protective

INFORMATION ON SERVICES

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Personal consultations by telephone. Appointments may be made by calling (503) 345-9855, or writing to the address below.

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Progesterone in Orthomolecular Medicine: $3.00 plus $1 postage.

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Hyperactivity
Pregnancy
Aging
Nursing
Reducing
Precocious Babies
Menopause

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AGE-RELATED OXIDATIVE CHANGES IN THE HAMSTER UTERUS

by

RAYMOND FRANKLIN PEAT

A DISSERTATION

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and the Graduate School of the University of Oregon
in partial fulfillment
of the requirements for the degree of
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INTRODUCTION

Sex and Aging

Theories of aging are historically closely associated with ideas about sexuality, and it is only in the twentieth century that the two have been habitually separated. The earliest tradition that was explicitly concerned with the nature of aging is that of the Taoist culture of China.

In China, experimental science was generally closely related to the Taoists' concept of natural balance and their desire for long life or immortality of the body. Deterioration of the body with age was considered to result from the imbalance of various factors, including masculinity and femininity, and attempts were made to find techniques or materials to cure disease, impotence, sterility, and aging itself. Ko Hung (a Taoist experimentalist) believed in the early fourth century A.D. that plant drugs would prolong life, and a compound of minerals and metals would give immortality. While other Taoists experimented on criminals, Ko Hung used plants and animals to study aging (Needham, 1956). Ginseng, which is rich in water soluble "anabolic" steroids (Bykhovtsova, 1970; Claus, Tyler, and Brady, 1970) is the best known of the Chinese herbs used for prolonging sexual vigor and

lengthening the life span. Recent studies indicate that ginseng promotes resistance to disease and stress, and increases the life span of rats (Yudkin, 1970; Grinevich and Brekhman, 1970). Eventually, in the Middle Ages, sophisticated methods were developed for extracting highly purified steroids from human urine, and these were used in treating senescence (Needham and Lu Gwei-Djen, 1968).

In the late nineteenth century, Brown-Sequard in France believed that testicular extracts could restore sexual, physical and mental vigor to old men. At the time of his announcement he was ridiculed and said to be deluded (Steinach, 1940). Up to the present time his claim is not generally accepted (Turner, 1966; Connors, 1969) because of the supposed insolubility of androgens in water, though testosterone is routinely used for postponing some of the symptoms of senescence in men. However, Brown-Sequard's claim seems reasonable enough, considering the abundance of fatty acids, lipo-proteins, and soluble simple proteins in the testes that would be able to make steroids soluble in water. Even the slightly polar nature of the androgens themselves (their hydroxyl and carbonyl groups) gives them a certain small degree of solubility in water.

The gonadal theory of aging (i.e., that degeneration of the gonads precedes and causes the degeneration of all other organs: Steinach, 1940) was generally discarded by 1940, but by the same time it was widely accepted that aging does involve changes in hormone controlled processes, and that hormonal insufficiency

or imbalance is likely to be intimately involved with senescence. Increasing biochemical sophistication was leading most investigators to look for subtler or more basic processes as the primary cause of aging. Gonadal degeneration is now more modestly considered to be one of many changes that occur as a result of a more basic process of aging, but its importance as a possible immediate cause of senescent sterility in the female is the subject of current investigations, which will be discussed below.

Physiological Theories of Aging

Two other 19th century ideas have remained viable, in modified form, up to the present. E. Metchnikof (1908) proposed that the basic cause of aging was connective tissue degeneration; the current version of the theory, viz., that aging results from molecular changes in collagen and structural changes in connective tissue, is now widely held, and fits the evidence well. He also (1908) believed that toxins from putrefaction in the intestine caused aging, and cited correlations between short intestines and long life spans. It has recently been suggested that polyamines, e.g., putrescine, with histamine-like effects, may be absorbed from the intestine and provoke reactions of an allergic type. Korenchevsky (1961) has discussed more recent versions of the "auto-intoxication" theory. Toxins of various types are known to induce auto-immune reactions (Nikolayev, et al., 1970), which have been implicated in

certain degenerative diseases and are believed by some to be a cause of aging, that is, the primary event in aging is presumed to be the appearance of antibody producing cells incapable of distinguishing self from other. Virus and diet have been implicated in auto-immune disease in NZB mice (Fernandes, et al., 1972). As a general cause of aging the auto-immune process would seem to be only a special case of somatic mutation, and A. Comfort (1969) has convincingly argued, in relation to Curtis's defense of the somatic mutation theory of aging, that somatic mutations are normally not numerous enough to account for aging, and that a cause prior to the mutations must be sought. What at first seemed to be a cause of aging turns out to be an effect of aging. D. G. Carpenter and J. A. Loynd (1968) similarly criticize the somatic mutation theory on the basis of the number of mutations that occur, but add that it fails to explain the effect of diet, and the changes that uniformly appear with age. P. Alexander and D. I. Connell (1963) have shown that the powerful mutagen ethyl methane sulphonate had no effect on the life-span of mice, in spite of causing more mutations than X-ray treatments which did shorten the life-span of mice, and conclude "that a non-genetic cause must be sought for the reduction of life expectancy which occurs in CBA mice after large doses of X-rays..." Although R. H. Mole (1963) has claimed that there is "no additive or synergistic effect of whole body irradiation by fast neutrons and natural aging," this does not apply to other forms of radiation, and some data will be mentioned below that show

a synergism between X-irradiation and dehydration in producing mutations and cell death. It is also interesting to note that Brachet (Bell, 1972) produced chromosomal abnormalities in amphibian eggs by merely heating the cortex. The evidence generally favors the idea that both aging and chromosome damage are physiologically caused, rather than the idea of Curtis and others that aging is produced by random somatic chromosomal mutations (Strehler, 1967).

The concept of accumulation of toxic material with age has the advantage of appearing to be a simple physical process that correlates very well with age (Dubina, 1970) and that could reasonably be expected to cause some of the functional changes associated with age, but again the process of metabolic detoxication, which can be assumed on the basis of various lines of evidence to decline with age, could account for the accumulation of toxic metals (Selye, 1967) and other materials with age. This criticism, however, is not as convincing as similar criticisms of other theories because of the peculiar vulnerability of the primary organ of detoxication, the liver, to toxins (Song and Kappas, 1968; Biskind, 1946). A very obvious positive feedback system must be involved, but the appropriateness of the feedback concept to a process of lifelong aging hasn't been demonstrated, and regenerative and higher control processes would add further complications. The capacity of heavy metals to act as catalytic centers, modifying the nature of the collagen system, suggests an overlap of the collagen and toxin theories of aging. The inactivation of enzymes by certain metals

(e.g., silver, mercury, arsenic) suggests that this theory would also have a degree of similarity to some of the somatic mutation and cybernetic theories of aging.

The theory of somatic mutations, resulting from background radiation or other random processes that would place the mutation as the first event in aging, is probably inadequate, as mentioned above, but there is evidence of some kind of physical change--possibly crosslinking--in at least some kinds of DNA, which increases with age (Hahn and Fritz, 1966). Increased melting temperature of DNA has been offered as evidence of a physical change assumed to involve inactivation of genes, but it is known that the melting temperature of another nucleic acid, transfer RNA, is very sensitive to ion concentration (Millar and Byrne, 1967). It might be that altered counter-ions are responsible for the observed change in DNA with age. It is known that general tissue concentrations and ratios of ions change with age (Kohn, 1971) and it seems that at least some of the change is intracellular (Friedman et al., 1965). Repetition of these experiments with purified DNA might settle this question.

An idea that used to be generally believed and that is still frequently encountered is that the nucleus is the center of all control processes in the cell and that therefore a change of cell function requires a loss of some kind in the information stored in the nucleus; an extreme form of the idea was the doctrine that only the germ line possessed a full complement of genes, and that somatic

differentiation occurred by selective loss of information. Gurdon's (1962) transplanting of nuclei from differentiated gut epithelium into enucleated egg cytoplasm was a clear refutation of that doctrine, since the nuclei allowed development into a late embryo. Although discredited for most organisms, the idea has given moral support to at least two theories of aging, viz., somatic mutations and Hayflick's idea (descended from Weismann's) of germ immortality - somatic mortality. Vegetative reproduction in plants is an obvious exception to Hayflick's principle of somatic cells being limited to a small number of divisions. Hayflick attempted to discount changes of the culture medium and "time" as factors inhibiting mitosis after a certain number of divisions, but time was measured with the cultures in the frozen state, which suggests that he has a strange conception of how time affects chemical and biological reactions. His demonstration that the medium didn't become progressively inhibitory was simply to put new fetal cells into a culture of cells that had stopped dividing, and show that they were able to divide. Strehler (1967) has shown that the number of divisions depends on the dilution factor. What Hayflick argues for is some kind of internal clock, designed to stop after a certain number of divisions, independent to a high degree of its environment. This internal clock concept is still held by some theorists to account for control of growth and differentiation, in opposition to the concept that cells differentiate in response to a series of inductive and inhibitory influences, which varies with time and their position in the organism. It has been demonstrated in Strehler's laboratory (1967) that physical restraint (an agar film)

that prevented mitosis allowed some kind of aging process to occur, in either the cell or the medium. Strehler (1967) also demonstrated, by labeling stem cells in skin, a capacity for division that is apparently unlimited, or at least is on the order of 100 times greater than the number set by Hayflick as a limit. Skin (Krohn, 1966) and mammary gland (Daniel et al., 1968; Daniel, 1971; Daniel and Young, 1971) transplant experiments have been used to argue for or against the idea of somatic cell mortality resulting from a fixed number of mitoses, but the arguments have been inconclusive in both cases. (Apparently it is generally tacitly assumed that transformed malignant cells are no longer somatic cells.) Hayflick's inhibition could be the result of either the presence or the absence of a chemical substance, or a physical factor, such as might be involved in Auerbach's discovery of reprogramming of lymphocytes by contact with other cells. Failure to consider the dilution factor is an important weakness in Hayflick's theory, just as it was in the (clonal selection theory) experiments criticized by Auerbach (1970).

Daniel et al. used mammary transplants in mice to argue for Hayflick's theory, but their assumption that immune reactions are not involved is not beyond question, and the experiments really just show that a tissue can outlive an organism. The purpose of the experiment was to study aging as it relates to an organism, but the survival of the tissue for several generations shows that the process involved in its eventual death is not likely to be

relevant to aging in the normal life span. They found, in fact, that the age of the tissue donor did not affect the lifespan of the transplants. The real significance of the experiment is to weaken the theory of programmed cell death as a factor determining the lifespan of an organism. The absence of an effect of donor age tends to support Kohn's belief that intracellular changes are not the most important factor in aging. More recently, Daniel et al. (1971) reinterpreted the results as showing only that the tissue "gradually loses its capacity to respond by proliferating to a hormonal stimulus that is relatively constant and which continues over a long period of time."

The inhibitory property of serum from old animals (Kohn, 1971) possibly relates to Hayflick's results, but it is very interesting from several other points of view. For example, it has been proposed (Comfort, 1964) that the cell loss which is typical of aging is the result of inhibition of mitosis by chalones and adrenalin. According to Bullough (1971) both aging and cancer result when inhibition is lost, and stress, by maintaining high levels of adrenalin, can prolong life. Delayed regeneration in old animals might relate to a high level of chalones. Adrenalin concentration may be elevated in old age, and sensitivity to exogenous adrenalin increases with age (Strehler, 1967; Frolkis et al., 1970) which is consistent with a high basal level, and with the concept of increased mitotic inhibition with age.

D. G. Carpenter (Carpenter and Loynd, 1968), a nuclear weapons engineer engaged in systems analysis of space weapons, has proposed an integrated theory, which consists in saying that many partially true theories of aging when taken together are more completely true. Regardless of his conclusions, his interest in feedback and amplification as part of an organism's control system is probably valid.

Sacher (1959) has proposed that the brain is the control system most relevant to aging, and the idea of neurone loss with aging is so popular that one of the most frequently repeated remarks about one's body concerns the supposed daily loss of 100,000 brain cells. The suggestion has even been made that the loss is so selective that it could be the basis for memory (Dawkins, 1971). Regardless of the idea's popularity and its good foundation in some insects, it certainly is not unchallenged (Comfort, 1964). Even the concept of age-related decline of mental function (e.g., the limit of learned reaction time or nonsense memorization) has been challenged by experiments using populations with equivalent occupations or an opportunity for relearning (Murrell, 1969). Analogous to the supposed decline in mental function with age (as distinct from disease) is Terman's observation that bright females suffer a severe loss of mentality at the age of 23, with the shift of occupation from student to housewife. The critics of the concept of brain loss with age sometimes claim that the brain is one of the most durable populations of cells, and that the "horizontal" averages of brain quality include a majority of diseased individuals,

that obscures the lack of effect of mere aging (Pfeiffer et al., 1968). However, this controversy is not necessarily essential to Sacher's idea of the brain as the most important control system in aging. Sacher's observation is that mass of brain correlates very well with length of life (1959). His belief is that the brain maintains biological equilibrium, and that with accumulated damage to the brain as a control system (whatever its nature) the organism would become increasingly unstable and die.

Sacher's correlation of brain size with length of life ("it's an advantage to have a brain, and a disadvantage to have a body ") recalls G. W. Crile's (1941) discovery of a close correlation between brain size and total metabolic activity (oxygen consumption per hour per animal) both between and within species. Crile's observation accounts in an odd way for the old approximate "two-thirds power" (actually 0.7 to 0.8 for most species) rule for increase of metabolic activity with increased body weight within a species (Florey, 1966), because this is approximately the proportion in which brain size increases with body weight (Lilly, 1963). The well-known actuarial data that show that short people live longer than tall ones might be relevant to this question, because of their proportionately larger brain size; the same would apply to the greater longevity of women. Energy production has been proposed as a crucial factor in life-span (Hershey, 1970; Calloway, 1971a).

Palladin (1964) has made a possibly related observation concerning "evolutionary level" (which in this case corresponded to brain size) and efficiency of oxidative phosphorylation. The efficiency of coupling was found to increase with higher evolutionary level, as well as with alertness. This observation suggests an interesting secondary factor to consider in relation to "rate of living" and Sacher's idea--the reason for Sacher's correlation might be metabolic efficiency, i.e., a less wasteful use of oxygen, possibly even a less destructive use of it.

The free-radical theory of aging has become very popular recently, probably partly as a result of radiation studies and partly because of the observation (Harman, 1968; Kohn, 1971) that antioxidants such as BHT added to the diet of mice increased their lifespan by several percent. It has been pointed out by other investigators that the mice ate less of the diet, probably because of the smell of the antioxidant, and that the restricted food intake alone could account for the increased life span (Comfort, 1972).

Restricted intake of calories has recently been found to slow the aging of collagen in rats (Everitt, 1971).

Relations of the Senescent Physiology to Other Physiological Processes

Other studies (Lee et al., 1952; Visscher et al., 1952) have shown that limitation of caloric and protein intake lengthens

the life span of mice, delays development of cancer in a susceptible strain, suppresses estrus and delays onset of both reproductive maturity and reproductive senescence. These observations will be discussed further below.

Smith and Soderwall's (1962) finding that supplementing the diet with vitamin E delayed reproductive senescence in hamsters, and similar observations in rats tempt one in this context to suggest that excess free radicals from an overactive metabolism are the agent of alteration in the collagen, which in turn leads to accelerated functional senescence. However, several problems exist for this interpretation, for example the relation between suppression or acceleration of sexual maturity and the onset of senescence, and also the idea that excess calories will necessarily increase the production of free radicals, which has not been established. The literature regarding free radical concentrations in living tissue is still in an early stage, as a result of the lack until recently of equipment that could measure EPR in the presence of water. This interpretation also fails to explain the observation that the amount of vitamin E required to maintain fertility increases steadily and drastically with age, being at 59 weeks 67 times the amount required by the 10 week old rat. Verzar and Ermini's (1970) observation of poor creatine phosphate recovery in old animals is interesting in connection with the creatinuria and low tissue creatine levels in vitamin E deficiency (Houchin, 1942) and the restoration of creatine kinase activity by vitamin E

administration (Matusis, 1971) and the fact that X-irradiation also produces creatinuria (Kozalka and Andrew, 1972).

Besides the functional complementarity of aging and vitamin E deficiency, there is an interesting similarity in their ability to produce lipofuscin, "aging pigment", or ceroid pigment (Kaunitz, et al., 1948). This pigment has been widely discussed as an example of intracellular crosslinking, and is assumed to be a "clinker," or product of metabolism that the cell is incapable of removing (Carpenter and Loynd, 1968). Florey (1966) has referred to the existence of this material in carp which are accustomed to living under ice at low oxygen tension and suggests that it may serve as an alternate electron acceptor in the absence of oxygen. (It is supposed that unsaturated fatty acids can serve as electron acceptor in yeast cells in the absence of oxygen (Warburg, et al., 1967).) Regardless of the accuracy of this guess concerning its function, Florey's observation at least points out the feature that is common to the various situations in which it appears: fetal liver (Goldfisher and Bernstein, 1969) has relatively low oxygen tension, and the disappearance of the pigment from the liver following birth would correspond to increased oxygen tension; aged cells are increasingly embedded in collagen, and probably experience reduced oxygen tension (Casarett, 1963); in vitamin E deficiency, there is extremely high oxygen consumption, which would tend to lower oxygen tension, and the pigment appears as a result of vitamin E deficiency (Kaunitz, et al., 1948).

That the intracellular oxygen tension is lowered by the high rate

of consumption associated with this deficiency is implied by the fact that muscular dystrophy can be induced in various experimental animals as a result of a vitamin E deficiency, and it has been demonstrated that raising dystrophic chicks in a high oxygen atmosphere suppresses development of the disease; similarly, restricted blood circulation also produces the disease, the most reasonable conclusion apparently being that low oxygen tension produces muscular distrophy, and a vitamin E deficiency "wastes" oxygen at a sufficient rate that oxygen tension is lowered in the tissue. Additional vitamin E allows animals to survive hypoxic conditions in a higher percentage than animals fed a normal or deficient diet (Telfer, 1954).

Bjorkerud (1963, 1964) has determined that there is NADH oxidase activity associated with the age pigment. NADH oxidase is, by consuming NADH, able to release one of the potential controls over fermentation (Racker, 1972) and, at the same time, can potentially reduce a large amount of the oxygen that enters the cell. Bjorkerud's observation would seem entirely consonant with the data concerning possibly impaired mitochondrial function in old age (Shikla and Kanungo, 1970) and the observations of Shock (1963) of undiminished oxygen consumption with age (in relation to active cell volume). This enzyme function should be elevated in vitamin E deficiency if the same system is really active in both cases. A microsomal NADPH oxidase is known to increase its oxygen consumption greatly in the absence of vitamin E, and <u>in vitro</u> pO_2 is rate limiting

in the peroxidative conversion of polyunsaturated fatty acids to a dialdehyde by this enzyme. Estrogen is known to induce an NADH oxidase. It has frequently been observed that many cells in the senescent hamster uterus are filled with pigment granules (Orsini, 1962). These granules apparently require estrogen and the absence of supplemental vitamin E if they are to form (Kaunitz, et al., 1948). Peroxidase, which is induced, or activated (Lucas, et al., 1955), by estrogen, and which is known to have an NADH oxidase function (Lucas et al., 1955; Beard and Hollander, 1962), may be involved. (Peroxidation is being widely studied in relation to both aging and cancer.) Catalase is apparently suppressed by estrogen, which suggests that peroxide, whatever its origin (it is universally associated with respiration, but it is not known how) is being spared for another function. In cancer, a condition similar to what is proposed here for aging exists, with low NADH combined with a "reducing environment" (Reid, 1965).

The proportionality, mentioned above, between onset of sexual maturity and age at which reproductive senescence, and even death, occur, has been recognized as a genetic, as well as a dietary, phenomenon by L. C. Strong (1969).

A well-known idea (Lansing, 1952) is that late maternal age tends to shorten the life-span of offspring; this seems to be in doubt even in the case of rotifers (Meadow and Barrows, 1971). (It is interesting that vitamin E happens to be necessary for sexual reproduction even in rotifers.) There is a general

belief that the effect exists in mammals, too (Lansing, 1947; Carpenter and Loynd, 1968); it is generally attributed to a higher rate of mutations in the older animal, which results in slightly defective offspring. Strong, Johnson, and Rimm (1963) found that late maternal age is associated with an earlier onset of sexual maturity in the offspring, which would be expected if the "Lansing effect" is true for mammals and if the reduction of life-span is associated with accelerated sexual maturity, as in the feeding experiments. However, Strong (1969) made the seemingly paradoxical observation that prolonged selection and inbreeding of the offspring of the 201-300 day maternal age group produces mice with fewer deviant traits, with fewer spontaneous cancers, and with longer life spans than those of strains produced by younger or older maternal age selection, and the earliest maternal age selection produced the poorest longevity.

Strong has rationalized this in terms of the concept of genetic homeostasis, which he associates with heterozygosity, as illustrated by the greater variability in age of first litter among homozygous than among heterozygous mice. He consideres the 201-300 day maternal age descent to represent a genetically more stable or homeostatic group. Many observations have been made relating the occurrence of cancer in Strong's mice to an excess of estrogen, but the evidence for the existence of high levels of estrogen is mostly indirect. Abnormal levels of estrogen in the strain could explain many of the effects observed, through an effect <u>in utero</u> (or through milk), without recourse to more complex genetic theories.

Blaha (personal communication, 1972) has expressed the opinion that hamsters probably don't have elevated estrogen levels in old age as do old rats which often have continuous estrus, in spite of the continued existence of 17-HSD which he says suggests the presence of estrogen (1972), but no measurements have been made of their circulating estrogen level. He has found elevated progesterone levels in old hamsters (1971), and proposes that it is the cause of their "delayed parturition." High levels of estrogen are considered to be responsible for the frequent endometrial hyperplasia in rabbits and have been suggested as a cause of the similar hyperplasia which frequently occurs in menopausal women (Cowdry, 1952; Dove et al., 1970).

Radiation or free radicals or both are sometimes believed to be responsible for the increased cross-linking of collagen assumed to be involved in the progressive increase with age in the melting temperature and melting contraction force of collagen, but it has been found that rat tail tendons of irradiated animals do not have the characteristics of aged rats' tendons. Whatever life-shortening effect irradiation has, and it does seem to mimic aging in certain ways, it doesn't appear to act by way of accelerated cross-linking in collagen.

B. W. Casarett (1963) proposed that radiation and other "non-specific" injuries lead to an "increase in density and amount of collagenous substance interstitially and in sub-endothelial

regions of arterioles. These changes constitute a temporal advancement in the increase of the histohaematic barrier and in the development of arteriolocapillary fibrosis, which are progressive processes in 'normal' aging. Eventually these processes cause progressive reduction in number of dependent parenchymal cells due to relative hypoxia and malnutrition." These ideas conform to the known effects of radiation, and he traces in detail the idea that both radiation and aging involve increasing isolation of the cells, which in itself constitutes an injury.

Brooksby, Sahinin, and A. L. Soderwall (1961) have reported that X-irradiation mimics certain features of reproductive senescence in hamsters, for example prolonged gestation equivalent to that of the senescent animal with 100 r whole body irradiation and, with all exposures used (100 to 700 r whole-body), increased connective tissue which infiltrates and thickens uterine muscles, glandular areas, and endothelial linings.

S. O. Brown, et al., have presented (1964) data that suggests that chronic low levels of radiation may accelerate the onset of reproductive maturity in rats. R. L. Brent (1964) observed some similarities between vascular clamping and maternal irradiation in effects on the fetus, suggesting the possibility that radiation may act partly through an effect on circulation or oxygen tension. Neonatal "heat" (Boling, et al., 1939) may result from hypoxia, since no hormonal basis is apparent. Estrogen and anoxia both improve resistance to irradiation (Katch and Edelman, 1964).

Radiation mimics estrogen stimulation in several other ways: vaginal cornification (Mandl and Zuckerman, 1956), uterine weight, estrus behavior, response to progesterone, etc., and appears to have its first physiological effect on respiration (Valentini and Hahn, 1971; Hahn and Ward, 1969). Ingram and Mandl (1958) claim that X-irradiated ovaries produce more estrogen than normal ones, without pituitary intervention.

Some of the other similarities between senescence and estrogen treatment observed in various animals are:

degree of corrugation and adhesiveness of luminal surface (Martin et al., 1970)

mitotic response in both lumen and stroma (Finn and Martin, 1969)

uterine weight

radiation resistance

vitamin E deficiency effect on uterine weight

vitamin E-estrogen antagonism on age pigments of uterus and other aging symptoms (Kaunitz et al., 1948)

catalase level (Baird and Samis, 1971; Adams, 1955)

Na/K ratio of cells (Friedman, et al., 1965)

basement membrane in reproductive organs (Fredricsson, 1969; Rowlatt, 1970)

increased tube-locking of ova (Connors, 1969; Greenwald, 1959)

chronic estrus (Bloch, 1961)

levels of uterine estrogen receptor protein (Kraay and Black, 1970; Trams, et al., 1971)

failure to implant, main embryo loss (Dreisbach, 1959; Connors, 1969)

tetrazolium reduction

oxygen consumption

oxygen partial pressure in lumen

Singhal and Valadares (1969) showed that very high levels of estrogen are required to restore ovariectomized old rats to their normal enzyme levels, which implies that high estrogen may be normal for old animals. In their mitotic response (Finn and Martin, 1969) to estrogen stimulation, however, old tissues showed greater sensitivity than did the young; residual bound estrogen might account for this, and the time allowed after ovariectomy might have differed in the two sets of experiments. Old animals have a similar high sensitivity to catecholamines (Frolkis, et al., 1970), which also can be interpreted as the effect of a high basal level. Catecholamines have also been associated with "oxygen wastage" (Raab, et al., 1962).

Metabolic rate (oxygen consumption) has long been known to decline steadily with age, although the steady state level of thyroxin in the blood (Gregerman, 1967) does not appear to change, but Shock et al. (1963) found that the loss of oxygen consumption per unit of tissue weight disappears when oxygen consumption is recalculated on a cell water basis. That is, there is a decline in the number or volume of active cells with age, as the mass of inert connective tissue increases, but there is no decrease in the rate of oxygen consumption of the remaining cells.

In spite of this evidence that oxygen consumption does not decrease generally with age, there is some evidence that mitochondria of various tissues (e.g., liver) lose efficiency, or decrease in number, or both, with increasing age (Shukla and Kanungo, 1970; Barrows, et al., 1960). Considering the oxidase activity of age pigment, it is possible that non-mitochondrial oxidation increases as mitochondrial oxidation declines.

Loeb (1939) has found remarkable similarities between the effect of excessive estrogen stimulation and senescence on the structure of the rat uterus. Both cause progressive increase in collagen deposits.

Arvay et al. (1971) have shown that stress accelerates the collagen changes of rat tail tendon and uterus, apparently acting through adrenal cortical hormones and estrogen.

These similarities in the effects of X-irradiation, estrogen, and senescence, suggest another experiment which found effects of X-irradiation and chemical carcinogens similar to those known for estrogenic stimulation. F. Devik (1963) has used the reduction of tetrazolium by skin cells to compare the effects of several carcinogenic and non-carcinogenic chemicals, and X-irradiation. Non-carcinogenic compounds caused a decreased deposition of the reduced form of the tetrazolium on the first day, while the carcinogenic compounds and the irradiation caused an increase, though the X-rays caused a more persistent increase. Damage to the mitochondria has been proposed as a common effect (Warburg, 1969; Devik, 1963),

but since it is generally believed that tetrazolium reduction is an indicator of dehydrogenase activity, all that is clearly indicated by these experiments is that carcinogens and radiation both activate or induce the dehydrogenases, or make more oxidizable substrate available. The increase is very rapid. Estrogen has very similar effects (several carcinogens are known to be estrogenic in the ovariectomized female (Turner, 1966; Needham, 1942)).

The fact that age, excess estrogen treatment, and irradiation all stimulate excessive collagen deposition, are sometimes associated with cancer development, can cause increased tetrazolium reduction, and produce similar effects on pregnancy, suggests that a new interpretation of the collagen theory of aging might be desirable. The enzyme system which synthesizes vitamin C, which is important in the development of collagen, loses activity with age, is inactivated by lipid peroxides and preserved by adding vitamin E, and also appears to be suppressed by estrogen (Patnaik, 1971; Chatterjee and McKee, 1965).

The failure of X-irradiation to increase cross-linking in collagen tends to weaken the free-radical theory of aging, and the mutation theory cannot explain satisfactorily either the generalized cross-linking or the generalized deposition of collagen. A common event, such as a metabolic pathway change, or a general interference with enzyme control systems, seems to be a more suitable alternative locus for the aging process, and it would seem especially suitable

if it were such as could be simply implicated in a self-stimulating (positive feedback) loop, tending to prevent reversal. For example, collagen accumulation could increase collagen synthesis or block its degradation. Casarett's scheme was of this kind, but he relied on the mere assumption that a non-specific injury would lead to increased density and amount of collagenous substance. What is lacking is information regarding the control of collagen synthesis, that could relate with each other the many specific stimuli that are known to accelerate collagen formation. Chvapil et al. (1970) found that in granuloma and in some organs in rats, prolonged hypoxia stimulates collagen synthesis and inhibits the synthesis of noncollagen protein, and enhances mitosis in fibrogenic cells. Hypoxia seems a likely common factor for the various non-specific injuries and provides a very simple positive feedback system.

A view of ionizing radiation's biological effects presented by Webb (1965) offers a radically different kind of action that would be at least potentially applicable to the intracellular control theory of aging proposed by Comfort and others (Comfort, 1969). Several Russian laboratories have proposed a similar mechanism to explain the biological activity of relatively low energy microwaves (Sharp and Paperiello, 1971). Webb found that, in bacteria, both the lethality and the mutagenicity of X-irradiation depended on the relative humidity of the atmosphere in which the experiments were performed, when the bacteria were suspended in an aerosol.

He showed that partial dehydration increased the bacteria's susceptibility to both effects. Various chemicals, such as inositol, that are known to protect proteins, cells, and organisms (Troshin, 1966) from destruction by various agents, were able to offset the effects of dehydration. Webb interpreted this effect in terms of the supposed ability of the molecules' hydroxyl groups to stabilize bound water which in turn would stabilize macromolecules, or larger structures such as membranes. A mechanism by which the pathway changes induced by estrogen, radiation, anoxia, and aging might result from a more or less direct action on intracellular water has been discussed elsewhere (Peat and Soderwall, 1971, 1972).

Alteration of the solvent properties of cell water could have very far reaching effects on the function of an organism (Atkinson, 1971).

One of the few factors, if not the only one, that shows a universal correlation with age, even before a many-celled stage is reached, is the concentration of water (Needham, 1964). Calloway (1971a, 1971b; Calloway and Kujak, 1966) has, from an analysis of the literature, shown that the water content of all organisms fits the same exponential curve on an absolute time scale. Thus, the tissues of a 24 month old rat contain roughly the same percentage of water as the tissues of a 16 month old human baby (both being about the same age from conception).

Intracellular ratios of sodium to potassium tend to increase with old age (Friedman, et al., 1967). However, the opposite occurs

during early development, approximately parallel to the decline in water concentration (Hazelwood, 1971). If Hazelwood (1971) and Wiggins (1970) and Szent-Gyorgyi (Baird et al., 1957) are correct in their theory of the control of the salt ratio, then one must assume that the intra-cellular water concentration, as opposed to the total organismic water concentration, would increase with age. This would be compatible with the known increase of mass and compactness of collagenous tissue with age, and with the data on the decrease of extracellular body water (thiocyanate diffusion space) with age (Kohn, 1971).

The conventional methods of measuring extracellular space have been criticized as over-estimating the true volume, at least in certain cases (Ling and Kromash, 1967). Whole organ concentrations of calcium, sodium, and chloride (Kohn, 1971) increase with age, and there are decreases in potassium, magnesium, and phosphate; Kohn interprets these changes as reflecting increasing extracellular space and decreasing cell volume, which accords with the microscopic picture, but there is also the likelihood (Friedman, 1967) that shifts of the same nature occur in the cell water itself.

If it is true that the intracellular water concentration is increased with age, it represents another feature of similarity among old cells, cancer cells, and estrogen stimulated tissue, since the others are already known to have a high water concentration (Hazelwood, 1971; Damadian, 1971).

The "Estrogenic" State

According to Pincus and Kirsch (1935) excess estrogen *in vivo* kills rabbit embryos at the blastocyst stage, but does not interfere with cleavage. Epinephrine prevents implantation in the rabbit, and hypoxia has been suggested as the cause (Auletta, 1971). The few measurements that have been made suggest that the increase of pO_2 in early pregnancy is delayed or inadequate in the senescent hamster, but since abnormally low pO_2 has been established in the cyclic senescent hamster, no special failure of a control system need be invoked to explain the difference at the time of implantation. These results suggest that it would be desirable to follow pO_2 levels throughout pregnancy, and especially at the time Thorneycroft and Soderwall (1969) observed increased resorption of embryos. Schultz (1967) has observed metabolic changes in old rats at day 12 during the period when resorption of embryos by old mothers occurred, which he interpreted as a shift toward estrogen dominance. Reduced sensitivity to deciduoma induction in rats has been attributed to high endogenous estrogen levels (Horikoshi and Wiest, 1971), and Schultz has also proposed high estrogen levels as the cause of low fertility in rats selected for small body size (1968) or high uterine metabolism (1965, 1966).

The literature provides many kinds of evidence supporting this interpretation, in spite of the popularity of the idea of estrogen insufficiency and, in humans and sometimes in experimental animals, of "estrogen replacement therapy" for menopause. The

concept of such therapy has been challenged, but probably the strongest reasons for holding the belief in estrogen insufficiency are a) elevated gonadotropins in senescence, b) decreased urinary estrogen excretion, and c) reduction, in some species, of the number of active follicles. In hamsters, the last reason is not relevant, since the number of follicles is normal (though the number of corpora lutea may be reduced (Thorneycroft and Soderwall, 1969b), but Steinach's (1940) view might be relevant for some species, viz., that interstitial cells multiply and increase hormone production whenever the germ cells are destroyed, e.g., by heat or radiation (Kennedy, 1970; Grindelund and Folk, 1962). Brooksby, Sahinin, and Soderwall's (1964) study of the effects of X-irradiation on hamster ovaries is consistent with this idea. Thung and Hollander (1967) have expressed a similar view: "In the ovary, the declining number of follicles is matched by the gradual evolution of proliferative cell groups.... These hyperplastic changes in senile ovaries are found in various species, but have been studied extensively in mice...." Some of the cells "....look very similar to the oestrogen-producing interstitial cells of the ovary. Actually, the occurrence of these cells in old ovaries is found to correlate with signs of increased oestrogenic stimulation."

The other reasons given as support for the idea of estrogen insufficiency are subject to various interpretations. The evidence in support of the ovary-pituitary feedback system, existence of which is the assumption behind the argument that elevated gonadotrophins

imply ovarian and estrogenic insufficiency, has been reviewed (Borth, 1967) and it was concluded that the evidence is fragmentary and weak. However, accepting the existence of such a control system at certain times, there is evidence suggesting that it may be inoperative in senescence, that is, that adrenal estrogens (Vinson and Jones, 1964) or ovarian estrogens (Mestwerdt, et al., 1972) may be overproduced in senescence, or adrenal estrogens may be overproduced when ovaries are removed (Diczfalusy, et al., 1964). Pineal involvement has been suggested as a factor in prolonged estrus in old rats (Meyer, et al., 1961). Aschheim (1964) suggests that the hypothalamus loses sensitivity to circulating steroids in senescence, which would be consistent with the effect of a vitamin E deficiency on nerve tissue, and possibly with the observation of P'an, et al. (1949), that pituitary extracts of vitamin E deficient rats caused greater gonadal stimulation in rats on a normal diet, than did extracts from rats on a normal diet. Drummond, et al. (1939) made similar observations. Orsini and Schwartz (1966) found that senescence apparently involves failure to release LH from the pituitary. Vitamin E has been considered to be anti-estrogenic (Shute, 1940; Evans and Burr, 1927a, 1927b, 1927c, 1928), as have various B vitamins (Biskind, 1949) and vitamin A, possibly by an effect on the liver. Since the amount of vitamin E needed to prevent symptoms of a deficiency increases greatly with age (Fuhr, et al., 1944; Emerson and Evans, 1940; Ames and Ludwig, 1964), most animals on a normal diet eventually show some signs of a

vitamin E deficiency. Since kidney resorption of the glucuronide of estrogens appears to be about zero (based on ratios of serum urinary estrogen conjugates in pregnancy), a small decrease in liver (or kidney, or other conjugating tissue) activity would tend to produce great increases in the amounts of unconjugated estrogens retained in the body. These estrogens would be almost entirely bound to proteins and lipids, but the equilibria of protein-estrogen binding are such that almost all of the body's unconjugated estrogens would be bound in the uterus, with smaller amounts in the vagina and mammary glands. Therefore, decrease of urinary conjugated estrogens (Poortman, et al., 1971) may directly reflect an increase of tissue-bound estrogens. Estrogen induces the estrogen binding protein (Kraay and Black, 1970), and post-menopausal women probably have a higher concentration of the binding protein than younger women (McGuire, et al., 1972; Trams, et al., 1971). Post-menopausal bleeding in women, often assumed to result from estrogen insufficiency, has been found to be associated with increased estrogen activity (Frampton, 1966). However, irritation, such as an intrauterine object causes, is also known to increase estrogen binding and uterine weight (Labhsetwar and Perser, 1972). Other estrogen-like effects of intrauterine irritation include luteolysis (Chatterjee, et al., 1971), increased oxygen uptake (Kar, et al., 1965, 1966), increased alkaline and acid phosphatase (Karkun, et al., 1969), and uterine weight (Malajiya, et al., 1970).

It is now generally accepted that senile estrus in rats (Meyer, et al., 1961; Bloch, 1961) and cystic hyperplasia in old rabbits (Burrows, 1949) result from excessive estrogen in old age. Some old mice have a prolonged proestrus (Thung, Boot, and Muhlboch, 1956). Cowdry (1952) has discussed this as a possibility in human cystic hyperplasia of the endometrium and other genital diseases which become very frequent after menopause. Dove, et al., (1970) have shown that urinary estrogen levels in post-menopausal women do not provide an index of the degree of estrogenic stimulation on the cytological level. However, Ward and Thyssen (1970) found that an elevated ratio of estrogens/androgens correlates with persistent karyopyknotic smears in post-menopausal women. Progesterone insufficiency has been suggested as the cause of menopausal disturbances and senescent sterility (Poulson, 1970; Matthew, 1949; Jones, 1970; Thorneycroft and Soderwall, 1969). Insufficient progesterone causes both failure to implant and congenital abnormalities, depending on the amount of progesterone given (Poulson, et al., 1965). Progesterone has been used in attempts to offset the anti-fertility effects of estrogen in rats, with conflicting results (Martin, 1962; Edgren, et al., 1961), and in cows, with good results (Otel, et al., 1968). Progesterone can even improve fertility after irradiation, which mimics estrogen (Valentini and Hahn, 1971). Even though it is generally accepted that, within certain limits, it is the estrogen/progesterone ratio which is important, rather than the absolute level, one would expect progesterone to be

incable of balancing the effect of a certain amount of estrogen because of its solubility or binding properties. The effective progesterone/estrogen ratio is sometimes placed as low as 2000:1, but several studies have suggested that it may be as much as 300,000:1 (or even higher) (Challis, et al., 1971; Nutting-Meyer, 1970), in which case it is obvious that the capacity of a tissue to absorb progesterone could easily be exceeded before reaching the concentration needed for the proper ratio. (Low solubility of progesterone has probably led to errors in protein binding assays: Clark and Gurpide, 1972).

In spite of Thorneycroft and Soderwall's suggestion, based on the size, number, and growth of corpora lutea in senescent hamsters, Blaha (1971) found serum progesterone levels to be elevated in old hamsters. However, without data on estrogen levels, this can be considered as possibly only a compensatory response to elevated estrogen. Leavit and Blaha (1970) attribute prolonged gestation (observed by Soderwall, et al., 1962, in senescent hamsters) to excess progesterone, through its supposed inhibitory effect on uterine contractility. Since the development of the embryo is retarded in older animals (Parkening and Soderwall, 1972; Connors, 1969) even before implantation, Blaha's theory seems inadequate to explain prolonged gestation. In vitro studies have shown permanent damage to the embryo from excess estrogen, but not from excess progesterone, yet both can interfere with cleavage (Daniel, 1964).

Glycogen deposits are diminished or at least delayed in their appearance in the decidual cells of senescent hamsters (Connors, 1969). This is usually attributed to estrogen insufficiency, but combined progesterone and estrogen appear to be responsible for increased glycogen deposition. Estrogen is known to activate glycogen phosphorylase (Takeuchi, et al., 1962), which under known intracellular conditions (that is, a ratio of Pi/glucose-1-phosphate of more than 3:2: Reithel, 1967) accelerates the conversion of glycogen to glucose. Glucose or oxygen deficiency (Mitchell and Yochim, 1968) or rapid growth (Needham, 1942) leads to disappearance of glycogen. Since sufficient progesterone is necessary for decidual cell differentiation to occur (Orsini, 1962) and excessive estrogen will entirely suppress the decidual cell response (Finn and Emmens, 1961), it seems that the delayed and diminished deposition of glycogen in the senescent animals' decidual cells should be attributed to a relative progesterone insufficiency (Pous and Comas, 1959), or even to excessive estrogenic stimulation. The higher sensitivity of the senescent uterus to induction of mitoses in ovariectomized rats (Finn and Martin, 1969) would be consistent with an excess of bound estrogen. However, vitamin E deficiency may also prevent glycogen accumulation (Butturini, 1949).

While progesterone (and the chemically related androgens) seem to have no toxic effect, organismically or cytologically,

estrogen has many deleterious effects when its concentration is too high, for example on the adrenals (Kimeldorf and Soderwall, 1947), on liver mitochondria (Gonzales-Angulo, 1970), on deciduoma formation (Finn and Emmens, 1961), on ova, in vitro (Kirkpatrick, 1971), on liver (Song and Kappas, 1969; Biskind, 1949), on fertility (Smith, 1926), and as a carcinogen (Needham, 1942). Korenchevsky (1961) listed depression, salt retention, renal degenerative changes, hypercalcaemia, hyperlipaemia, and epithelial hyperplasia as other toxic effects.

Estrogen treatment is known to be able to cause liver damage, and prolonged treatment with estrogen lowers the activity of the "mixed function oxidases" (Song and Kappas, 1968; Biskind, 1946). Chronic estrogen treatment lowers UDP - glucuronyl-transferase activity (which is important for removal of estrogen from the body) and also lowers the activity of -glucuronidase, after first raising its level (Wakabayashi, 1971). Many liver toxins can lower the liver's capacity to inactivate estrogen (Biskind, 1946). Since urinary estrogens may be 1000 times more concentrated than those in the blood, the importance of conjugation in the liver for regulation of hormone concentration is obvious. Nutritional deficiencies are able to interrupt the liver's conjugation of steroids (and other substances), and vitamin E deficiency is known to be involved in various liver diseases (Schwarz, 1949). Since the requirements for vitamin E increase with age (Fuhr, et al., 1949), liver function

would tend to become increasingly precarious, to the extent that it depends on the vitamin. Most of the measurable symptoms of vitamin E deficiency have a precipitous onset (Fitch, 1968), appearing and becoming extreme within a few days or a few weeks, though serum tocopherol may not have been detectable for many months. Such a physiological process might be involved in the sudden "menopause" when it involves many large physiological changes, but a sudden onset of infertility without other sudden changes would suggest that a simple threshold of survival conditions of the embryo may have been reached.

Estrogen seems to lower the intracellular K/Na ratio, possibly causing the cell's "trans-membrane" potential to become lower (Spaziani and Suddick, 1967; Jones, 1968, 1972; Goodland, 1953). Such a change in salt ratio (Orr, et al., 1972) and in electrical potential (Cone, 1970) apparently is very closely involved with the regulation of DNA and RNA synthesis and with mitosis. Oxidative phosphorylation (Strickland, et al., 1955) is apparently necessary for maintaining high intracellular K/Na ratios though possibly not for maintaining the resting potential (Ling, 1962), so it is possible that estrogen might have its early action either on the cytoplasmic structure (Nemetchek-Gansler, 1967; Peat and Soderwall, 1972), i.e., producing a permeability or phase change, and thus affecting oxidation by modifying structural relationships and diffusion rates and solubilities, or on oxidative phosphorylation, with a phase change

(i.e., a salt ratio change) resulting from a reduction of the energy charge. Merely incubating uterus in Eagle's medium mimics estrogen action (Mueller, et al., 1958), and hypo-osmolarity duplicates some effects (Adams and Haynes, 1969). Progesterone has an opposite effect on sodium retention (Tomlinson, 1971; Jones, 1972). Sex hormone effects seem to be universal and specific; even yeast "sexual" types are selectively affected by the mammalian hormones (Takao, et al., 1971; Yanagishima, et al., 1970).

The best known scheme for estrogen action (Jensen, et al., 1968; Mueller, et al., 1958) suggests that estrogen binds to a cytoplasmic "transport" protein and then enters the nucleus where it modifies the chromosomes so that certain mRNAs are transcribed, leading to synthesis of new proteins which then produce all other effects by membrane and enzymic changes. This theory ignores the fact that lipids are the first substances (by several hours) to show net synthesis (Mueller, 1958), and the observations that salt ratio changes are sufficient to initiate, stop, or modify synthesis of DNA and RNA (Allfrey, et al., 1964; Lezzi, 1969). Engel (1970) suggests that certain enzymes have estrogen affinity sufficient to make them "receptors." Although the 9.5S and the 4-6S "receptors" are not known to have enzyme activity, this may simply reflect the fact that the leading investigators of these proteins are not interested in their potential enzyme activity.

The Problem of Senescent Sterility and Oxygen Wastage as its Immediate Cause

Several of the best established events in the aging process -- changes in collagen, water, salts, pigment, and certain enzymes -- form a constellation, at least part of which reappears in several other physiological states, which may have useful similarities to aging: vitamin E deficiency, low oxygen tension, estrogen stimulation, and radiation damage. (Muscular dystrophy, and possibly even myocardial "oxygen wastage," may also be related conditions.) Two of these states--vitamin E deficiency and radiation damage, have been well studied in their relation to reproductive senescence. This thesis will pursue the concept that low oxygen tension is a probable immediate mechanism in reduced fertility, and that the above mentioned constellation of factors, possibly initiated by estrogen but also a self-stimulating process common to other physiological states mentioned, is a prior cause of reproductive senescence.

Senescent hamsters ovulate seemingly normal eggs in normal numbers. There is a much greater loss of embryos at the time of implantation among old hamsters than among the young (seven times greater, according to Thorneycroft and Soderwall, 1969a). Some loss does occur by later resorption (two times greater than young: Thorneycroft and Soderwall, 1969b), and some ova seem to be delayed in passage through the oviduct in the senescent animals (Connors, 1969), but their greatest difference from the young is at implantation

(Connors, Thorpe, and Soderwall, 1971). It has been fairly well established in several species (Adams, 1965; Finn and Martin, 1969; Talbert and Krohn, 1966; Biggers, 1969; Maurer and Foote, 1971; Finn, 1970) that the aged uterus or its hormonal environment is more likely to be the cause of sterility than the aged ova. Lack of adhesiveness and lack of nutritive support are two possible aspects of the uterus that have been considered as causes of aged sterility. Although differences of surface structure and content of glycogen and certain enzymes are known, it is difficult to argue that these are decisive. For example, even if glycogen stores are low, blood glucose should provide a substitute; if estrogen dominance leads to rapid consumption of glucose by the uterus, lactate should be available. Blaha (1964) found early embryos apparently adhering to the uterine epithelium in senescent hamsters, and only later did they disappear. The requirement of the embryo for molecules of three or four carbonsat the two cell stage disappears by the blastocyst stage (Brinster, 1971; Biggers, 1971). However, there is a large increase in oxygen consumption by the embryo at the blastocyst stage, both in rate and in total quantity. (This seems to be true for all vertebrates.) Needham (1931, 1942) reviewed the work of Warburg, Loeb, and others on the relation of pO_2 to respiration and development, and for the organisms considered development was retarded and respiration inhibited by moderately low pO_2. In the normal animal, according to several studies in

rats (Yochim and Mitchell, 1968; Yochim, 1971), the luminal pO_2 increases sharply at this time, just preceding implantation, and remains high as far into pregnancy as measurements have been made. This coincidence of increasing demand and increasing supply suggests that a failure of supply may be critical, since no substitute for adequate oxygen is known. Glenister's (1970) observation that embryos in tissue culture will develop farthest in an atmosphere of 30% to 50% oxygen suggests that oxygen may be the limiting factor in implantation. He found that implantation occurred in vitro irrespective of the physiological stage of the endometriums or the presence or absence of added hromones. Glenister found that hamster blastocysts would not attach to hamster endometrium which was arranged in the form of a "well", which suggests that the slightly greater diffusion distance in this configuration (which was unnecessary when he used larger rabbit embryos) might have been responsible for the failure to attach. It is known that the shape of the vessel can govern the rate of blastocyst development in vitro (Winterberger, Torres and Daniel, 1971). Some of the embryos in several species are retarded in their development in old animals. With even a moderate oxygen consumption rate, the pO_2 drops sharply with the distance the oxygen must diffuse (Longmuir, 1958). The apparent Km for oxygen of cytochrome oxidase is high, but the actual Km of the enzyme is almost infinitely small (Boag, 1970). The apparent Km for oxygen of intact cells has been found to increase

with the diameter of the cell (Longmuir, 1958) and if this rule applies to ova and blastocysts, then the Km of these must be very high: possibly close to the pO_2 of capillaries.

According to Yochim's calculations, the uterine blood flow does not increase as much as uterine respiration and uterine mass following estrogenic stimulation, with the result that the tissue becomes relatively hypoxic. The increased proportion of connective tissue (Brooks, Sahinin, and Soderwall, 1964) would probably have a similar effect. Parkening and Soderwall (1972) have presented evidence for impaired capillary permeability in old hamsters at the time of implantation, and suggest that this may be responsible for delayed development of the blastocyst and its failure to implant. Damage to uterine circulation prevents implantation in mice (Senger, Lose, and Ulberg, 1967; Wigglesworth, 1964; Bruce, 1971).

With these considerations, it would seem appropriate to look for the causes of senescent loss of fertility in the physiological differences that exist between the young and the old uterus. The cyclic uterus would reveal basic differences that exist as a function of age, independent of the effect of embryos (McLaren and Menke, 1971). (Embryos at different stages of development might make the meaning of pO_2 much more complex. Even with only the electrode consuming O_2 at the luminal surface or in luminal fluid, the problem of a local gradient and different diffusion rates is a possible source of error.) Besides oxygen tension, related factors will be

investigated, including rate of oxygen consumption, reductive activity, and some specific enzymes that are relevant.

METHODS AND MATERIALS

Animals

Hamsters (Mesocricetus auratus) which had been maintained under conditions of controlled light periods and partially controlled temperature and housed in individual cages were used in these experiments. They were fed lab chow pellets and lettuce; from August to December, 1971, they were given a vitamin supplement, including vitamin E. Two age groups were used: "young", three to six months old, and "senescent", thirteen to sixteen months old.

When the whole uterus was to be used, the animals were given 0.5 ml of sodium pentobarbital solution (50 mg/ml) by intraperitoneal injection, and when measurements were to be made in vivo 0.25 ml/100 gr. body weight was given. Animals were followed through at least 2 estrus cycles, using the method of Orsini (1961), and were used on day 4 of the cycle.

For enzyme studies, the uteri were removed, blotted and gently stripped to remove fluid, and weighed. Wet weight is used in all experiments, since large increases in collagen would make dry weight or protein basis misleading. The decreased water content would tend to offset increased collagen of old tissue. For the tetrazolium assay, 40 mg. pieces of whole uterus were blotted, weighed, and

immediately dropped into the tetrazolium solution at incubation temperature. When endometrium and myometrium were to be assayed separately, the uterus was opened by cutting one side longitudinally, and placed on a cool glass surface, where the endometrium was quickly removed by scraping and placed in cold saline until weighed. The tissue was homogenized in one ml. of saline for each gram of fresh tissue.

For respiration measurements, the tissue was prepared as above except that instead of being homogenized, it was cut with small scissors into pieces about 0.5 mm in diameter. Pieces of approximately 10 to 15 mg. of endometrium, myometrium, or whole uterus were blotted on dry glass and quickly weighed, then returned to cold Krebs-Ringers before being cut. Thechopped tissue was immediately placed in 2 ml. of cold Krebs-Ringers in the respirometer flask, or in the electrode chamber.

Oxygen Consumption

GILSON MANOMETRIC METHOD: 10 to 15 mg. of uterine tissue prepared as described above was placed in 3 ml. of Krebs-Ringer solution, pH 7.1 in a manometer flask, with 0.2 ml. of concentrated KCl solution in the center well with a filter paper wick, and allowed to equilibrate for 5 minutes at 36°C before recording oxygen consumption. Readings were made at 5 or 10 minute intervals for one hour. In some cases, concentrated sulfuric acid was added to the vessel side-arms.

BECKMAN CLARK ELECTRODE METHOD: 0.2 ml. of Krebs-Ringers solution was injected into the recording chamber and allowed to reach 37°; 10 mg. of tissue, prepared as described above, was placed in the chamber and the Beckman Clark electrode was inserted, and recording was begun immediately, using the Backman 160 Physiological Gas Analyzer and a Varicord recorder.

Luminal Oxygen Tension

Some measurements were made using a Beckman platinum microelectrode inserted into the uterine lumen through an 18 gauge arterial needle. Most measurements were made by cutting an opening on the anti-mesometrial side of the uterus about 0.5 cm below the uterotubal junction and inserting the bare microelectrode directly into the lumen. One horn of the uterus was exposed at a time through a small incision in the back, so the same animal could be used for more than one measurement. Thirteen cycling animals were used, and two on day 4 1/2 of pregnancy. Insertion of the electrode through the vagina may allow air to enter.

Triphenyl Tetrazolium Chloride Reduction

Forty mg. of fresh tissue was dropped into 4 ml. of a 0.5% solution of TTC in 0.1 M phosphate buffer, pH 8.5, and incubated one hour at 37°C. The tissue was then removed and left

in 4 ml. of reagent grade acetone until all color was removed. As a blank control, 40 mg. of fresh tissue was placed directly into 4 ml. of acetone. The color intensity was recorded photometrically (at 475 nm.) and the quantity of formazan present was determined by comparison with known quantities of formazan in acetone.

Enzymes

TOTAL LDH. 0.1 ml of enzyme solution (supernatant fluid of the homogenate) was diluted with 1.0 ml of saline and 0.1 ml of this solution was added to Sigma Standard Substrate, incubated for 30 minutes, developed with Sigma Color Reagent, and optical density was measured in a Beckman Model B spectrophotometer at 570 nm. wavelength.

LDH ISOZYMES. Enzyme solution was prepared as above, except that 0.1 ml of the enzyme was diluted with phosphate buffer, 0.1 M, pH 7.5, and heated to 57°C to inactivate the heat sensitive isozyme 1 (liver or muscle isozyme), and another 0.1 ml was heated to 65°C to inactivate all isozymes but the relatively heat stable isozyme 5 (heart isozyme). The heated enzymes were then treated as above, and their activities were compared to an unheated sample. Some samples were separated by electrophoresis and stained with Sigma color reagent and substrate.

Special care must be taken with the homogenate for LDH measurement, since the M_4 isozyme is cold-denatured (Zondag, 1963).

β-GLUCURONIDASE. Phenolphthalein glucuronide (0.01 M) was used as a substrate, and incubated at 37° in an acetate buffer at pH 4.5 for 1 hour, with 0.1 ml of the same enzyme solution used for LDH assays (Fishman and Green, 1956; Talalay, Fishman and Huggins, 1946; Fishman, Springer, and Brunetti, 1948). Released phenolphthalein was made visible by raising the pH to 10.5 with glycine buffer, and measured in the photometer at 540 nm. Fixed sections of uterus were also treated, for approximate localization of the enzyme.

PEROXIDASE. P-phenylenediamine (0.01 M) was used as substrate, and incubated at room temperature. The photometric measurement was made every minute during the raction. 0.1 ml of the same enzyme solution as above was used. Fixed sections of uterus were also stained with p-phenylenediamine for general localization of peroxidase activity.

CATALASE. Using 0.01 M hydrogen peroxide as substrate, 0.1 ml of the enzyme solution described above was placed in a respirometer flask with 2 ml. of substrate solution (in phosphate buffered saline, pH 7.5, 0.15 M) and the rate of oxygen evolution was recorded. With the same substrate concentration, both enzymes should reach the same total amount of oxygen generated, though at different times, but the concentration of H_2O_2 used inactivates both enzyme solutions in about the same length of time, leaving some substrate unchanged when the reaction stops from enzyme damage.

Animals to be used in NMR studies of estrogen influence were injected subcutaneously with 5 µg of estradiol in albumin solution three days before using, and ovariectomized animals were prepared at least a month before use. Whole uteri were kept in cool saline until they were placed in NMR vials.

Assays

BOUND-ESTROGEN ASSAY, BROWN-ITTRICH FLUORESCENSE METHOD. (Lunaas, 1962). Whole uterine homogenate was extracted with 2 volumes of acetone, which was partially evaporated, and placed in fuming sulphuric acid, and then extracted with 4 ml of methylene chloride. This was placed in quartz cuvettes, and a Hitachi Perkin Elmer MPF-2A fluroescence spectrophotometer was used to scan at 565 nm while exciting with u.v. at 546 nm, using slits #5, and sensitivities 5 and 6.

DYE COUPLING METHOD. (4-amino-6-chloro-m-benzenedisulfonamide.) Urbanyi's method developed for pharmaceutical use was applied to a methanol extract of the uterine homogenate (Urbanyi and Reim, 1966).

BIO-ASSAY. Whole uteri were extracted in acetone (Jakubowska-Naziemblo, 1969), which was evaporated and the extract resuspended in 1% ethanol in saline solution. Half of this was injected as 2 subcutaneous doses (1 ml each) on consecutive days into each ovariectomized animal. Their uteri were inspected and weighed two days after the second injection.

UTERINE AGE PIGMENT EXTRACTION. Whole senescent uteri which had been cleared in benzyl benzoate and which were heavily pigmented were soaked in reagent grade diethyl ether or pyridine until the solvent was slightly colored, about 24 hours. Ether or pyridine extracts of old uteri were scanned at visible frequencies in a Beckman Model B Spectrophotometer, and at ultraviolet frequencies in a Cary 14 ultraviolet photometer.

Uterine Weight, Water Content, and Diameter

After weighing the whole fresh uterus, pieces of 50 to 75 mg of whole uterus, or 10 to 20 mg of endometrium, or 50 to 100 mg of myometrium were occasionally taken for dehydration and determination of wet weight/dry weight ratio. Representative slides of fixed uterine cross sections were measured to determine overall diameter and thickness of myometrium and endometrium.

Vitamin E Treatment

Three animals were given 125 units of vitamin E once a week for six weeks, orally, and were then used for oxygen tension measurements.

NMR Spin Echo of Tissue

Recently removed uteri were examined in a Nuclear Magnetic Resonance Specialties Spin Echo Spectrometer, at 25 megahertz.

Inspection of Harderian Glands

The eyes of recently killed hamsters were pushed aside and the tissues of the eye sockets were examined under long-wave ultraviolet light for red fluorescence.

Uterine Age Pigment Extraction

Whole senescent uteri which had been cleared in benzyl benzoate and which were heavily pigmented were soaked in reagent grade di-ethyl ether or pyridine until the solvent was slightly colored, about 24 hours. Ether or pyridine extracts of old uteri were scanned at visible frequencies in a Beckman Model B spectrophotometer, and at ultraviolet frequencies in a Cary 15 ultraviolet photometer.

Statistics

Differences between means were evaluated by Student's t test, with Cochran's approximation to the Behrens-Fisher correction for samples of different variation when necessary.

RESULTS

> It is really rather strange that human beings are normally deaf to the strongest arguments while they are always inclined to overestimate measuring accuracies.
>
> --A. Einstein

OXYGEN CONSUMPTION. The uteri of forty-six animals, twenty-three young and twenty-three senescent, were studied by the Gilson manometric technique, and six (three young, three old) by the Beckman oxygen electrode method. The mean QO_2 (in μl O_2/mg. wet weight/hour) were:

Senescent	Young	P
3.7	2.5	$<.05$

This is not a high level of significance, but the limitation is probably inherent in the method (Jusiak, 1970). Finer discrimination can be achieved by using an indirect method such as TTC reduction, assuming that these two events closely correspond to each other, as indicated by Cascarano and Zwifach (1955). The problem of ammonia production will be discussed below (under Oxygen Consumption, in Discussion).

LUMINAL OXYGEN TENSION. Cycling animals:

	Senescent (5)	Young (5)	Vitamin E treated (3)
Range, mm Hg	0-2	4-8	6-12

The oxygen tensions measured in the senescent uteri are in the range known to limit *in vitro* respiration, and also to limit development of cultured embryos (Needham 1931), but the exact oxygen requirements of embryos are not accurately known, since oxygen tension is normally measured only in the gas phase. The effective Km for oxygen increases with increased cell diameter (Longmuir, 1957), and the viscosity of the surrounding medium must also have an effect. The early period following ovulation is likely to be similar in both the regular cycle and following mating. This difference in pO_2 could easily account for the early retardation observed in senescent hamsters' embryos, such as lagging cleavage and delay in loss of the zona pellucida. The established lag in uterine changes (Connors, 1969; Stockton, 1972) suggests that this difference in pO_2 may become even more distinct around the time of implantation, when respiration is even higher, and the likelihood of damage even greater, but the fact that the lumen no longer exists at this time makes it necessary to depend on indirect evidence. If it can be generally accepted that TTC reduction does accurately reflect the QO_2 of a tissue, then a complete study of the differences in uterine reductive capacity between old and young animals should be done on each day of pregnancy, to build on the very suggestive work that has been done on rats of different ages by Schultze (1967).

One young and one senescent hamster on day 4 1/2 of pregnancy were used in an attempt to study the luminal oxygen tension directly, and the pO_2s measured were 4 mm Hg in the senescent, and 15-40 mm Hg in the young. However, the procedure caused tremendous disruption

of the tissues. Since the closure of the young lumen is believed to be firmer than that of the old animal, this very large difference could probably be at least partly attributed to greater bleeding in the young. Nevertheless, differences such as these would be expected on the basis of decreased oxygen consumption of implantation sites, and the senescent lag in factors related to implantation.

TTC REDUCTION.

	Senescent	Young	P
% Transmittance at 475 nm	33	48	<.01

These values are equivalent to approximately .05 and .03 mg formazan per sample, respectively (22 animals). In a group of three young litter mates and three old litter mates, the variability was much less (P <.001).

β-GLUCURONIDASE. Mean % transmittance at 540 nm after one hour incubation:

Senescent (3)	Young (3)	P
34	20	<.01

Sections showed a generalized pale stain, except around blood vessels, where it was very intense.

PEROXIDASE. Mean % transmittance at 540 nm and at 90 seconds:

Senescent (4)	Young (4)	P
59	66	<.05

Sections showed intensely stained granules about 5 μ in diameter distributed throughout, but especially in the endometrium, and a

very intensely stained endometrial epithelium; a few larger areas, about 20 by 80 microns, were more lightly stained; these may have been blood vessels.

CATALASE. Mean μl O_2 at 5 minutes:

Senescent (4)	Young (4)	P
78	105	$<.05$

UTERINE WEIGHT.

	3-6 months	14 months	P
Mean	385 mg	592 mg	$<.001$

Mean ratio dry weight/wet weight:

		Senescent	Young
25 animals	myometrium	1:4	1:6
12 animals	endometrium	1:6.5	1:6.6

The greatest increase of thickness was in the myometrium, but the endometrium also appeared to become thicker with age.

Estrogen Assays

BROWN-ITTRICH FLUROESCENCE METHOD. Five old and three young uteri showed a significant difference in fluorescence at the frequencies used for the oxidation product (or products) of estrogen. The shape of the spectrum was similar to that of estrogen products, and to that of the standard solutions used, within the resolution, which was very poor under these conditions of sensitivity and frequency.

Mean intensity of fluorescence (in arbitrary units):

Mean S (5)	Mean Y (3)	P
52	14	$<.01$

Estradiol Standard

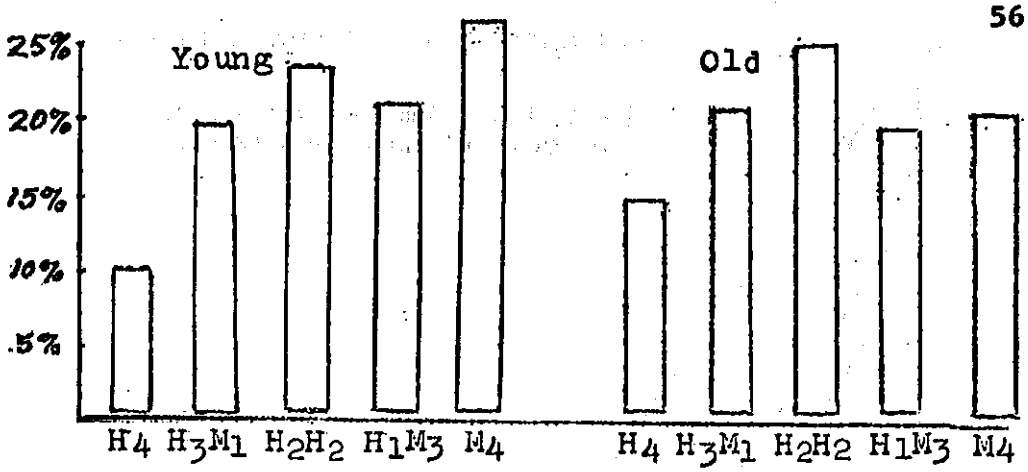
1 µg	10 µg
19	27

DYE COUPLING METHOD (4-amino-6-chloro-m-benzenedisulfonamide): Rather than the red product resulting from condensation of estrogen with the dye both young and old gave a yellow product; the old gave a more intense yellow color. This would suggest either that there was no estrogen in the extract, or that there were other materials that condensed with the dye more easily. The technique was discarded as an estrogen assay, but the fact that there was an age-dependent difference, and that bile pigments similarly condense to form diazo products, suggest that the product's spectrum should be compared with known bile pigments similarly condensed.

BIOASSAY. Since this method was intended to assay for "estrogenicity" bound in the uterus, extraction was made in acetone, in which estrogen is highly soluble. An effect on the uterine weight was the intended object of investigation. However, it was noticed that after two injections (containing the extract of 1/2 an old uterus) the ovariectomized recipient had red fluorescence around one eye. This typical Harderian fluorescence has been reported not to occur in ovariectomized animals unless estrogen

has been administered, although injection of porphyrins into intact rodents can cause increased secretion, which has led to the concept that the gland may concentrate and secrete porphyrins produced elsewhere, rather than synthesizing them (Figge, 1947). No difference in uterine weight was observed.

AGE PIGMENT. The age pigment spectrum of certain tissues has been studied by Strehler (1967) and Karnaukhov (1971). Strehler reported increasing but homogeneous absorption at higher frequency ultraviolet, but Karnaukhov found several peaks of absorption around 260-280 nm (an acetone extract in petroleum ether) in nerve and salivary gland extracts. The uterine pigment, extracted in ether, shows increasing absorption at shorter wavelength (especially below 250 nm), except for a peak at 280 nm, similar to one observed in a blood extract and to one peak in Karnaukhov's extract. This is consistent with the suggestion of Orsini and Meyer (1962) and Deno (1937) that the pigment is related to blood or hemosiderin, but the nearly smooth absorption curve could represent a complex mixture. The peak at 280 nm is lost in a methanol extract.



Typical electrophoretic distribution of isozymes

Mean % of H_4

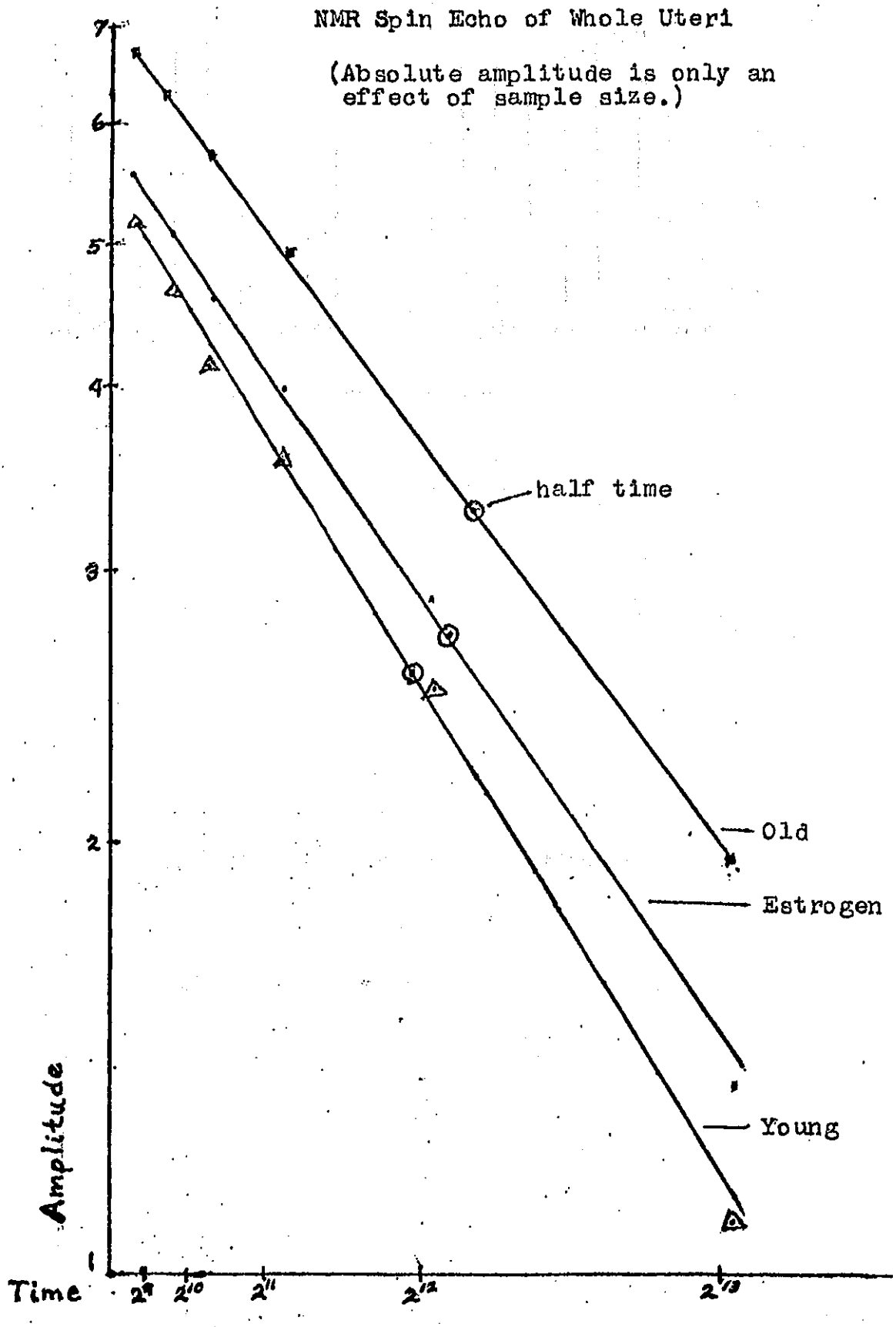
	S	Y	P
12 animals (6 old, 6 young)	14.3	10.7	.05

Total LDH Activity in B-B Units per ml:

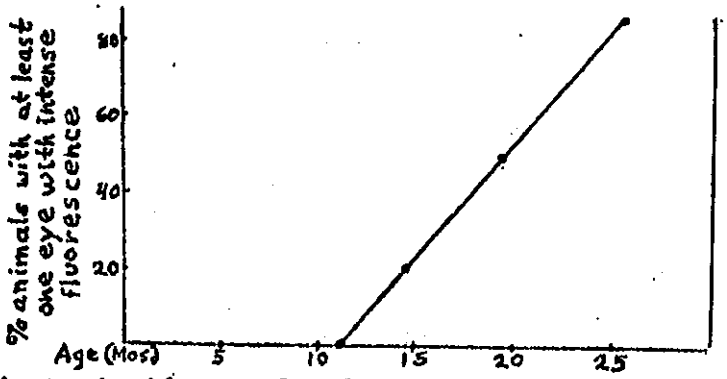
S	Y	P
1700	1950	.05

NMR Spin Echo of Whole Uteri

(Absolute amplitude is only an effect of sample size.)



Harderian Fluorescence



Approximate incidence of red eye fluorescence with age in months. 25 animals.

NMR Spin Echo

The NMR spin echo results are similar to those of Damadian (1971) comparing tumor with normal tissue, and of Hazelwood (1971), comparing fetal with mature tissue. The results suggest that senescent uterine water is more bulk-like than that of young uterus, as tumor and fetal tissue water is more bulk-like than that of normal and mature tissues.

DISCUSSION

Every statement implies a metaphysic.
--A. N. Whitehead

The Paradigm Problem

Even seemingly simple and "straight-forward" problems and solutions are ultimately questions of probability, and interpretation is present in the most "objective" treatment of a question (Tart, 1972). A more complex problem requires a more complex context if a similar degree of "objectivity" is to be maintained. Whenever a paradigm is left, the question of interpretation becomes more apparent.

This thesis begins by questioning the paradigm of "aging as decline" of hormone concentration and metabolic rate. That paradigm was based on certain gross and organismic observations, and is valid with regard to androgenic, luteal, and certain adrenal hormones, at least in most mammals, and with regard to whole animal oxygen consumption per unit of tissue, and probably even with regard to mitochondrial respiration. However, it lacks generality. Highlights from a large literature regarding the physiology of aging are presented in the introduction, to show that a contrary, and much more general, paradigm exists, which can be stated

approximately as "in aging and other distress conditions, typical shifts of metabolic pathways occur." Measurements that only seem peculiar when considered in the former paradigm, may be definitive in the latter. The typical shifts of metabolism include:

a) "damaged respiration" in the sense of a decreased efficiency of phosphorylation, or excessive hydrolysis of ATP, by high ATPase activity, which can result from mitochondrial damage;

b) compensatory glycolytic phosphorylation;

c) given mitochondrial damage and NADH production in glycolysis, a necessary step in compensation is the oxidation of NADH, for example by LDH, or peroxidase, or "age-pigment-related NADH oxidase." Either lactate formation, or oxygen consumption, or both, or another kind of oxidation, must increase if glycolysis is to proceed.

This paradigm forms an interpretive link between the various "distress conditions," and suggests that low oxygen tension will be a factor in these various conditions. The literature on mammalian loss of fertility under many conditions, e.g., X-irradiation, estrogen treatment, adrenaline treatment, senescence, vitamin E deficiency, progesterone deficiency, intrauterine devices, etc., is remarkable for the great similarities that exist in such diverse conditions. Estrogen action is the most common and easily manipulable of these conditions, and so each of the other conditions tends to be

described as "estrogenic." Knowledge regarding the states in which estrogen may be bound within the uterus is not adequate to provide a sound basis for its extraction and unambiguous assay. Whether these conditions that prevent gestation actually increase estrogen concentration in the uterus, or merely mimic it, is still debatable. The available metabolic information about the various "distress conditions" indicates that oxygen wastage is likely to be a common factor; data on embryos' requirement for oxygen *in vitro* show that oxygen deprivation *in utero* could be responsible for pregnancy wastage. The new paradigm suggests the hypothesis of loss of fertility through excessive reduction of oxygen, as a normal feature of aging, as well as in the various other "distress conditions." All aspects of the hamster uterus that have been measured are consistent with this. The old paradigm does not unambiguously predict any of the observed age changes. To make it do so requires a complex series of *ad hoc* assumptions, each one to explain away as "non-estrogenic" a change which to this point had been considered to be estrogenic. One clear prediction that it makes is that the senescent uterus will *not* have an elevated metabolic rate. This is refuted by the observations, especially the TTC reduction.

Another clear prediction made by the old paradigm is that senescent sterility and estrogen-induced sterility will not act by the same mechanism, since senescent sterility is conceived of as an effect of estrogen deficiency, exactly the opposite of an estrogen

excess. However, the data show that senescence lowers oxygen tension, just as estrogen treatment does.

It is remarkable that, in spite of *in vitro* studies that show sensitivity of mammalian embryos to changes in oxygen tension, the issue has been almost entirely ignored in studies of fertility, and has never previously been considered in relation to senescent sterility. Even percentages of oxygen higher than atmospheric can be limiting to embryos implanting *in vitro*, suggesting that implantation is especially sensitive to oxygen deficiency. Implantation is also the main point of damage in the various "distress conditions," as far as the question has been investigated.

A paradigm by definition is open-ended enough to allow for further development, and so can never be overturned by data or reasoning, but it can become increasingly untenable. The smaller question, however, of whether oxidative changes are adequate to account for embryonic retardation, non-implantation, and resorption can be more decisively answered, because the less complex question calls on a less complex interpretive context.

The observations require rejection of the view that an oxygen deficiency cannot occur in the uterus from common physiological causes. Hypoxia has been proposed as the cause of abortion following vasoligation, but it has been generally believed that only such gross interference with circulation could produce sufficient hypoxia. That the cause can be physiological is indicated by the increased metabolic rate.

Beyond this, the observations characterize the senescent uterus as being in a very common physiological state, which can be called a "distress state." The causal relation between age and the other states is discussed on the basis of the literature. Senescence is physiological, and the physiology is such that sterility must result.

The correspondence of the changes in the senescent uterus to changes in the other distress states supports the view that the changes are patterned, paradigmatic, coherent and meaningful metabolic changes. Although the pathway details are not completely known, the existence of compensatory glycolysis and non-mitochondrial oxidation have been well established in various tissues.

The Senescent State

There is considerable evidence that the estrogen/progesterone ratio, or estrogen/17-keto steroid ratio, increases with age, at least in mice, rats, rabbits, and women, and that this change has metabolic effects similar to treatment with exogenous estrogen. However, irritation, low thyroid, excessive copper absorption, etc., probably could increase the estrogen effect without necessarily affecting the concentration of circulating estrogens. To find in senescence the metabolic state associated with estrogen treatment is interesting more for the possible effects of this state on functions such as implantation, than for its corroboration of a suspected excess of estrogen. The generality of this "distress state" of

metabolism is intrinsically interesting.

Enzymes

Many enzymes, including ATPase, spermidine synthetase, alkaline phosphatase, NADH-oxidase, β-glucuronidase, sulfatase, peroxidase, hexokinase (Gross, 1961), malate dehydrogenase (Wilson, 1969), glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase (Schmidt, et al., 1967), lactic dehydrogenase, and ornithine decarboxylase (Kaye et al., 1971), change in activity under the influence of estrogen, but a few are especially important in relation to oxidative metabolism. An apparent increase of cytochrome oxidase following estrogen treatment turned out to be peroxidase (Lucas, et al., 1955).

LDH was considered to be an especially suitable enzyme to study in relation to implantation because its total activity and isozyme composition are known to reflect oxygen concentration and degree of estrogenic stimulation, and to relate to the tissue's disposition of lactate and pyruvate (Johansson, 1966; Battelino, et al., 1971; Goodfriend and Kaplan, 1964; Dawson, et al., 1964). The enzyme can also function as a potential "transhydrogenase" system (Sanwal, et al., 1970; Young, 1961), and thus is in a position to regulate the glucose-6-phosphate oxidation pathway of carbohydrate metabolism. Also, the equilibrium

$$\text{lactate} + NAD^+ \rightleftharpoons \text{pyruvate} + NADH + H^+$$

implies that as the reaction proceeds toward lactate formation, the pH will tend to rise. In many tissues the ratio of lactate/pyruvate is much smaller than the chemical equilibrium, probably because of oxidative competition for the NADH (Olson, 1963). Restricting oxygen would probably allow the reaction to move farther toward equilibrium, with a consumption of protons. Elevated pH tends to weaken other controls (e.g., the inhibiting effect of ATP, involved in the Pasteur effect) over phosphofructokinase (Racker, 1972) which is an important control point in glycolysis. Waddell (1969) has pointed out that the addition of glucose to cancer cells tends to raise the intracellular pH, as the cells form large amounts of lactate. High pH has been observed to increase the rate of lactate formation without increasing respiration (Tobin and Mehlman, 1971). In aged rats, intracellular pH may be elevated (Comolli, 1971) as well as lactate production in certain tissues (Angelova-Gateva, 1968). The NAD^+/NADH ratio also controls the rate of glyceraldehyde-3-phosphate oxidation (Racker, 1972). LDH is thus in a position to exercise extensive control over glycolysis, possibly providing a mechanism for interfering with the Pasteur effect (which is decreased under the influence of estrogen: Greenstein, 1954). The LDH isozyme ratio may be of importance not only for determining the availability of pyruvate for oxidation, but for regulating other pathways. (Considering the low pO_2 of senescent or estrogen dominated hamster uterus, and the requirements of spermatozoa for oxygen - Nevo, 1965 - the X isozyme in male

producing spermatozoa - Stambaugh and Buckley, 1970 - may relate to the lower proportion of males in senescence or estrogen treatment: Hahn and Hays, 1963).

In the presence of very active NADH-oxidase, pyruvate and lactate might also have a "coenzyme" function in relation to this enzyme. Peroxidase, which is "induced" by estrogen, has an NADH-oxidase function (Lucas, et al., 1955), and this activity is also found in association with age pigment (Strehler, 1967).

There is a slight decrease of total LDH activity in old animals, probably not significant considering their higher proportion of connective tissue and collagen.

Oxygen tension regulates the isozyme ratio, both in vitro and in vivo (Clark and Yochim, 1971; Yochim and Clark, 1970; Fujisawa, 1969; Johansson, 1966). Citric acid cycle intermediates can retard the formation of isozyme "M" by chick heart muscle cells in culture (Cahn, 1969), but oxygen tension has its isozyme inducing effect regardless of the presence of metabolic inhibitors, including fluoroacetate, potassium cyanide, 2, 4-dinitrophenol and sodium amytal (Johansson, 1966). Because of this, it has been speculated that oxygen might act directly on the genes regulating LDH isozyme synthesis, but other methods of control, such as preferential degradation (Pruitt, 1971; Greengard, 1967) might be more fruitful to investigate experimentally, especially considering the greater lability of the "liver" isozyme, both in heat and cold (Zondag, 1963;

Kreutzer and Fennis, 1964). Direct action of oxygen or peroxides on the labile isozyme, or an effect involving sequestering of the stabilizing coenzyme, NAD, might be mechanisms for regulating isozyme proportions. The H_4 isozyme seems to be the most lipophilic as well as the most stable, and M_4 the least lipophilic (Kabara and Konvich, 1972). This result is implicitly predicted by the theory which relates cytoplasmic phase changes to control of enzyme activity (Peat and Soderwall, 1972).

Finding the H_4 isozyme increased with age leads to at least two or three questions:

1) Does enzyme induction by oxygen relate to the rate of consumption of oxygen, rather than to oxygen tension itself?
2) If the function of this isozyme is to save some pyruvate for another use, rather than converting it to lactate (Lehninger, 1970), is carboxylation to oxaloacetate that use?
3) Would it lead to a situation in which (because of H-LDH's inhibition by high concentrations of pyruvate) pyruvate carboxylase tended to become rate limiting for glycolysis?

Although no mechanism is suggested, it is interesting that the age shift of isozymes is opposite to the shift which occurs in pregnancy, as early as day 5, when uterine oxygen consumption is known to decrease (Battelino, et al., 1971).

β-Glucuronidase is increased in liver, uterus, kidney, and other tissues by injection of estrogen (Fishman, 1950) or various

poisons, and this effect has been likened to the induction of detoxifying enzymes in the liver by their substrates. Levvy (Karunairatnam and Levvy, 1949) has offered the contrary interpretation that β-glucuronidase is merely involved in tissue proliferation, regardless of what causes the proliferation. Prolonged estrogen treatment causes an eventual decline in β-glucuronidase, as it does of the mixed function oxidases (Song and Kappas, 1968). Its decline with age in the hamster uterus thus is consistent with the view that estrogen tends to dominate uterine metabolism in senescence, but of course doesn't imply that this is what occurs. However, if its normal function in the uterus and other tissues is to conjugate and remove estrogen to prevent estrogen toxicity, then its absence in the senescent uterus would suggest an explanation for other physiological changes that occur in the uterus with age. If estrogen no longer turned over in the uterus, then a much smaller supply could raise the uterine content. Estrogen treatment is known to "induce" larger amounts of the estrogen binding protein (Kraay and Black, 1970), as well as reducing the progesterone binding capacity of the uterus (Armstrong and King, 1971). Post-menopausal women have at least as high a concentration of uterine "estrogen receptor" protein as do younger women (McGuire, et al., 1972; Trams, et al., 1971).

β-Glucuronidase is known to have an in vitro transferase function (e.g., transfer of glucuronic acid from phenolphthalein to an alcohol) besides its common hydrolytic function (Fishman and

Green, 1957). It has been shown to have a slow synthetic function *in vitro* (Florkin, 1940). Fishman (personal communication) feels that an *in vivo* conjugating (transferase) function is plausible, considering the similar role of a "hydrolytic" enzyme such as glucose-6-phosphatase. β-Glucuronidase is so abundant in smooth endoplasmic reticulum that it is considered likely to be a structural protein (Wakabayashi, 1970).

CATALASE. Catalase activity of the uterus is interesting because it is believed to relate to the cytochrome system (Deisseroth and Dounce, 1970), is lower in the female, at least in some species (Adams, 1965), and since either its rate of synthesis or rate of degradation appears to change with age in mouse liver (Baird and Samis, 1971). The fact that its activity is lowered by riboflavin deficiency (Adams, 1965) and by serum or tissue extract from animals with tumors (Nakahara and Fukuoka, 1959), and is lower in females, suggests that its level will correspond to the amount of energy derived from mitochondrial oxidation. A similar extract is an abortifacient. The lower level in the aged uterus would not be particularly interesting if oxygen consumption were lower in that tissue. Since oxygen consumption tends to be higher, low catalase activity suggests that the oxidation may not be occurring in the usual way.

PEROXIDASE. The fact that estrogen activates the NADH-oxidase function of peroxidase, which itself is "induced" by estrogen (Lucas, *et al.*, 1955; Yokota and Yamazaki, 1965; Jellink and Lyttle, 1971; Temple, *et al.*, 1959; Hollander and Stephens, 1959; Beard

and Hollander, 1962) suggests that in the uterus peroxidase may be involved at an early stage in the process of cell activation by estrogen. Vitamin E, which is known to inhibit peroxidation, has anti-estrogenic effects, including inhibition of the formation of the estrogen-dependent uterine age pigment, which is associated with NADH-oxidase activity, and which is generally considered to result from peroxidation of lipids and proteins (Elftman, et al., 1949).

VITAMIN E. Two classical symptoms of a vitamin E deficiency are increased tissue oxygen consumption (Houchin, 1942) and anemia (Fitch, 1968). The degree of stability of erythrocytes in the presence of oxidants, such as hydrogen peroxide, is an indication of the vitamin E status of the animal. Vitamin E has an anti-oxidant function, but other properties are also believed to be involved in its vitamin activity. It increases the viscosity of protein solutions (e.g., albumin), apparently by causing a more extended conformation of the protein. Such a physical or mechanical property, as well as a chemical anti-oxidant property, could be involved in its anti-hemolytic effect, and in its ability to stabilize other "membrane" systems such as lysosomes (McCay et al., 1971). It lowers the extractability of muscle proteins (Matusis, 1970). The enzymes of vitamin C synthesis in microsomes are inactivated by lipid peroxides, and preserved by added α-tocopherol (Chatterjee and McKee, 1965). Estrogen's effects on vitamin C synthesis,

β-glucuronidase (of lysosomes), and pigment formation may be produced by a common structural event. Uterine age pigment requires estrogen for its development, but vitamin E treatment prevents its formation (Kaunitz, et al., 1948; Atkinson, et al., 1949). If hemes, or other porphyrins, are related to the lipofuscins or age pigments, they may be responsible for the NADH-oxidase activity that Bjorkerud (Strehler, 1967) found associated with the pigments. The same hemolysis which leads to vitamin E deficiency anemia could therefore also be responsible for the increased oxidation of vitamin E deficiency. Since hypoxia stimulates porphyrin synthesis (Falk, et al., 1959), oxygen wastage by porphyrins would tend to be a positive feedback process. The oxidase activity of age pigment granules is cold-inactivated (Bjorkerud and Cummins, 1963), which is consistent with the theory of pathway regulation by "structural temperature" (Peat and Soderwall, 1972). If estrogen's action is intrinsically related to a hypoxic state, this could also explain the fact that porphyrins are synergistic with estrogen, and similarly could explain the occurrence of porphyrins mainly in female and cancer-prone rodents (Strong, 1942; Figge, 1942). Vitamin E is known to lower serum bilirubin related to liver damage (Schwarz, 1949).

The circulatory availability of oxygen, as well as the metabolic disposition of oxygen, may be directly related to the vitamin E status of the animal. Adaptive hyperemia in several glands

has been found to result from the action of peptide kinins, produced by proteolytic kallikreins (Schachter, 1969). Small molecule inhibitors (e.g., Trasylol, ε-amino caproic acid) are known, as well as the protein inhibitors, of the kallikreins and other proteolytic enzymes (cathepsins, trypsin). Age, X-irradiation, and estrogen have been implicated in various ways in proteinase inhibition. The "Shute test" (Shute, 1937; de Oliveira, 1949), a measure of the level of serum proteolytic inhibitory activity, clearly shows that a vitamin E deficiency increases the inhibition of proteolytic enzymes. The presence of inhibitors would tend to suppress formation of kinins, the local "inflammatory" vasodilators, and would also interfere with clot removal.

The hamsters that were given vitamin E in very large doses showed chronic leucocytic vaginal smears, as in rats given daily doses of progesterone (Labhsetwar, 1970).

A vitamin E deficiency causes muscles of rabbits (Morgulis and Osheroff, 1937) to increase their concentration of "extracellular" ions, especially Na^{+}, Cl^{-}, and Ca^{++}, suggesting a possible loss of organic ions, as well as an energy loss: creatine phosphate may be largely responsible, since vitamin E deficiency causes creatinuria.

The observations of Thorneycroft and Soderwall (1969) regarding fewer and smaller corpora lutea in senescent hamsters may relate to the observations of Lecoq and Isidor (1949) that vitamin E deficient rats have no corpora lutea.

Progesterone's effect on Na^{+}, Cl^{-}, Ca^{++}, and water is similar to that of vitamin E, and opposed to estrogen's effect. The most sensitive demonstration of vitamin E's anti-estrogen effect is probably Lecoq's (1949) on uterine chronaxy.

Vitamin E requirements increase with age (Fuhr, et al., 1949; Ames and Ludwig, 1964; P'an, et al., 1949; Emerson and Evans, 1940) and a deficiency acts mostly to block implantation (Blandau, et al., 1949).

Oxygen Consumption

A likely source of error in measuring tissue oxygen consumption (besides the problem of balancing cell damage in thin slices or minces against limited diffusion in thicker slices: Jusiak, 1970) is in neglecting to account for other gaseous metabolites (Dudka, et al., 1971; Maharajh and Walkley, 1972) than oxygen and carbon dioxide, of which ammonia is likely to be the most important by far. Tashiro (1922) observed ammonia production in nerve and muscle, which increased when the tissue was stimulated. Needham (1942) wrote that ammonia is not likely to be produced by embryonic tissue unless sufficient carbohydrate is not available, implying that it results from protein catabolism. A popular contemporary argument (Lowenstein, 1972) is that ammonia emission results from the activity of adenylate deaminase, but in many cases glutamic dehydrogenase seems a more likely enzyme. In estrogen stimulation protein synthesis and turnover are accelerated (Mueller, 1968); glutamic acid is an important link between carbohydrate metabolism and

proteins, and is also closely related to synthesis of pyrroles. Aspartate, however, seems to be the first amino acid synthesized after estrogenic stimulation (Jervell, et al., 1958), probably by amination of oxaloacetate (Barker and Warren, 1966). Glutamate dehydrogenase may have alanine dehydrogenase activity when dissociated into subunits. Estrogen can regulate this dissociation and change of activity, probably by increasing the supply of NADH (Tomkins, et al., 1961). Estrogen-increased L-alanine pyruvate conversion by this form of glutamate dehydrogenase would account for some of the diversion of pyruvate into protein synthesis. Lacking carbohydrate, a reversal of the reaction could form pyruvate, with a high rate of protein catabolism and production of ammonia. (A shift of the enzyme activity away from glutamate dehydrogenase may spare glutamate for synthesis of δ-levulinic acid, and porphyrins.)

Senescent uterus has reduced glycogen levels in pregnancy (Connors, 1969), and if this lack of glycogen exists in the cycling senescent uterus, or if the rate of metabolism is high in relation to available carbohydrate, aged uterus may release more ammonia than young uterus. In vitro, where small glycogen deposits may be quickly consumed and no external glucose is provided, the tissue with the highest metabolic rate will probably release the most ammonia, and if this is not taken into account, the manometric method will read this as diminished oxygen consumption. In the first measurements, samples often showed negative "oxygen consumption," and this occurred more often with senescent tissue, especially

myometrium, and probably was intensified by delay in preparing the tissue. Although the literature on uterine oxygen consumption does not mention this problem, it may be a general factor in measurements of oxygen consumption. When sulfuric acid was added to the vessel side arms, oxygen consumption measurements became consistently positive and rates became more consistent, especially in the case of senescent tissue.

Dissolved oxygen measurements would tend to show alteration in the opposite direction when ammonia is released, so additional measurements were made in the Beckman apparatus. No removal of ammonia is possible in this case, so the data should be considered only in relation to the manometric data, unless it can be assumed that the much shorter time needed to get measurements eliminates the factor of ammonia production.

Increased oxygen consumption by estrogen-activated tissue does not imply increased mitochondrial oxidation, coupled to phosphorylation or not. Lucas et al. (1955) determined that what had been assumed to be elevated cytochrome oxidase activity was actually the NADH-oxidase activity of peroxidase. Wilson (1969) reported the puzzling observation that estrogen increased the activity of only malate dehydrogenase of all the citric acid cycle enzymes, and that others may have decreased. It is interesting that MDH is one of the few enzymes known to increase in some tissues in senescence (Finch, 1972). The carboxylation of pyruvate to oxalo-

acetate, followed by amination to form aspartic acid (Barker and Warren, 1966; Jervell, et al., 1958)may have its equivalent in this situation, viz., production of oxaloacetate for amino acid formation.

Barker, Nielson, and Warren (1966) claim that lipid synthesis, mediated by $NADP^+$, regulates the hexose monophosphate shunt. (Elsewhere it has been suggested how a cytoplasmic phase change could accelerate lipid synthesis: Peat and Soderwall, 1972). They found that the specific activity of glucose-6-phosphate dehydrogenase decreased significantly during an early period in which G6P and 6PG were being oxidized at an increased rate. Activation of either lipid synthesis or oxidation of NADPH would be able to stimulate this pathway.

Oxygen Tension

The measurements of intrauterine pO_2 that have been made with the Beckman microelectrode inserted through an 18 gauge arterial needle (Yochim and Clark, 1971; Mitchell and Yochim, 1968, 1969b; Salderini and Yochim, 1967) are apparently inaccurately high. The sharp end, and additional thickness, possibly cause still-oxygenated blood to be freed into the cavity surrounding the electrode tip, where it would not be subject to oxidation by the tissue. The cyclic variation of about 20 mm Hg pO_2 could be a further artifact, since the electrode itself reduces oxygen and will quickly

lower the oxygen tension of a small volume of fluid that is not stirred. The end of the needle immobilises a few microliters of liquid. Periodic contractions of the uterus would replace the fluid in the tip of the needle with fresh blood (or other oxygenated fluid produced by introducing the electrode) from elsewhere in the lumen. This procedure gave measurements in the hamster's uterus that were about the same as those obtained by Yochim and others in the rat, except that instead of one minute cycles, in the hamster the cycles were about three to four minutes long. Different means or maxima determined by this method would therefore reflect indirectly the rate of oxygen consumption by measuring the level of oxygen present in the blood which is released into the lumen. The rate of oxygen consumption would not be entirely unrelated to tissue pO_2 (Yochim, 1971), but it would present an entirely false picture of the conditions experienced by the pre-implantation embryo.

Using the "bare" electrode (with stainless steel jacket, but no needle around it) with a diameter of 1.0 mm and a blunt tip, a much lower pO_2 was measured, and there was no cyclic change that could be recorded. The oxygen tension is so low that an accurate absolute measurement is extremely difficult, but relative measurements of differences between animals can be easily and clearly made. The oxygen tensions observed are lower than any known mammalian tissue except cancer. Senescent animals' uteri had a pO_2 in the range of 0-2 mm Hg, young animals in the range of 4-8 mm Hg, and

vitamin E treated senescent, 6-12 mm Hg. The color of the uterus varied from maroon in the old animals to pale pink in the vitamin E treated animals; young animals' uteri were bright red.

At such low oxygen tension it might be advantageous to have hemoglobin with high oxygen affinity; it has been reported that sheep with hemoglobin A (with higher than normal oxygen affinity) are better able to withstand the abortifacient effects of estrogenic pasture than are other sheep (Obst and Seamark, 1971). A lower "unloading tension" would correspond to a lower tissue oxygen tension, with possibly adaptive effects, such as a more controlled or gradual release of oxygen. Oxygen consumption decreases at implantation sites in the rat uterus at the time of implantation (Surani and Heald, 1971), and this probably causes a rise in pO_2 to levels the embryo requires. Progesterone by counteracting estrogen, may be the cause (Goodland, et al., 1953). As early as the fourth day of pregnancy there are greatly increased obstructions in the uterus, probably from increased adhesiveness of the epithelium which at this time is closing over the blastocysts. Even the "bare" electrode has to be forced if it travels more than a centimeter from the opening, and obviously is causing luminal bleeding. The force required was such that at one obstruction the electrode passed entirely through the wall of the uterus. Before hitting an obstruction the pO_2 reading was 40 mm Hg, which might have been high because of being near the opening, though the soft and abundant endometrium formed

a seal. Beyond the obstructions the pO_2 measured 5-10 mm Hg, or about that of the vitamin E treated cycling hamsters. The average blood would be expected to have more oxygen than the respiring tissue but if the deeper stromal or myometrial tissue were respiring faster than the implanting epithelium, bleeding might cause a lowering of pO_2.

Yochim's system of measuring uterine luminal oxygen tension with an arterial needle may be measuring something equivalent to the "bulk" pO_2 in organ culture, i.e., possibly uterine fluid that has been contaminated with oxygenated blood or gas introduced with the needle, so they are possibly correct about the effect of pO_2 on LDH isozyme proportions in the uterus, which they compare to the effects in cultured uteri.

However, the pO_2 at the surface of the cell in culture, where the effect of pO_2 on LDH isozymes is to be studied, will be much lower, because of an O_2 gradient in the unstirred layer. A bare electrode, able to contact the epithelial tissue in the uterus, and less likely to cause bleeding, would probably more closely approach the pO_2 actually experienced by tissue either <u>in vivo</u> or in culture.

The pO_2 Yochim's group measured would not, according to Needham's review (1931), be low enough to approach limitation of embryonic development. However, when the lumen "surface" pO_2 is measured, by the bare electrode, the tension is seen to be close to that which limits respiration and development of embryos; the actual pO_2

the embryo experienced in the experiments reviewed by Needham is not known, nor is the actual pO_2 in the old hamster's uterus, since it is at the extreme lower limit of the measuring system's capacity. A better technique is needed, to determine the real minimum.

TTC Reduction

The reduction of triphenyl tetrazolium chloride is considered to reflect dehydrogenase activity (Racker, 1955; Novikoff, 1959) or the cell's reductive capacity, including substrate availability, and is believed to be one of the most sensitive indicators of estrogenic stimulation. It is known to accurately correspond to QO_2 in many tissues (Cascarano and Zweifach, 1955). Martin (1959) has reported that the TTC reducing response of the ovariectomized mouse vagina to exogenous estrogen is linear in relation to dosage from about two picograms of estradiol per mouse up to about one microgram. Estrogen increases phosphorylase activity (Takeuchi, et al., 1962) and ATPase activity, so would tend to release inhibition of glycolytic enzymes while providing increased amounts of glucose. Ammonia is a very effective activator of phosphofructokinase, and may be produced by cell activation (Lowenstein, 1972). The production of NADH would therefore be increased. The earliest effect of estrogen may be on glycolysis, rather than on respiration (Roberts and Szego, 1953). Since estrogen causes "induction" of peroxidase, which has NADH oxidase activity (for which estrogen serves as a coenzyme: Beard and Hollander, 1962), at least part of the increased

NADH would tend to reduce oxygen by this short-circuit route, increasing oxygen consumption without necessarily increasing usable oxidative energy production. That is, an extramitochondrial uncoupling of oxidative phosphorylation could occur through these known enzymic effects of estrogen. Whatever the mechanism, increased oxygen consumption must lower the pO_2 of a tissue if circulation doesn't increase proportionately. According to Yochim, et al. (1971) circulation doesn't increase as fast as the mass of tissue increases, under estrogenic stimulation. With the rapid "uptake" of water (or possibly metabolic production of water) immediately after estrogen treatment, the average distance of cytoplasm from capillaries must increase, which would possibly decrease the efficiency of tissue oxygenation.

The fact that the senescent hamster uterus shows distinctly increased TTC reduction is probably the best evidence that senescent sterility is the result of an active physiological process (or malfunction). Schultz (1964, 1965, 1966, 1967, 1968) has found that strain differences in rats suggestive of estrogen differences correlate with fertility and TTC reduction. Selection for large bodies produced low uterine TTC reduction and large litters, while selection for small bodies produced high uterine TTC reduction, and small litters. He also found increased TTC reduction at the time of senescent litter loss by resorption in rats.

Racker's (1955) "nothing dehydrogenase" of well-dialyzed protein fractions, which give a strong nitroprusside reaction, reduces NAD

or NADP without the addition of substrate, and the reduced nucleotide can then reduce tetrazolium. Racker and others have guessed that protein SH groups are the source of this reducing capacity. The present tendency is probably to assume that starches or fats contaminate the protein fraction and provide the reductive capacity. However, G. Ungar (1957, 1959) has presented some evidence to support the view that cell excitation involves an increase of protein SH groups, resulting from conformation changes or "partial denaturation" after excitation or hormone treatment. The technique of determining uterine protein SH concentration is very hard to use reliably, but might eventually be useful to study the more exact nature of the uterine reducing capacity which changes with age and estrogen treatment.

Age Pigment

Uterine "age pigment," which develops in the presence of estrogen and vitamin E deficiency (Kaunitz, et al., 1949), is not noticeably soluble in ethanol, benzene, benzyl benzoate, acetone, or chloroform, but is highly soluble in alkaline pyridine solution which is an excellent bile pigment solvent, and is partly soluble in ether, which is also a solvent for certain bile pigments (With, 1968), and the spectrum is somewhat similar to that of a blood extract. The presence of an ether soluble fraction of bile pigment of a

certain magnitude in human serum is considered to be indicative of cancer (With, 1968). Bjorkerud (1964) has observed that age pigment has NADH oxidase activity, and contains the heme group. Aged uteri (Zinkat, 1931) contain remarkably large amounts of iron, which might be bound by the hemes. The fact that the pigments appear under conditions in which red blood cells are hemolyzing rapidly, further supports the possibility that they are porphyrin-related (Gyorgy and Rose, 1949). Bjorkerud (1964) also observed that this NADH oxidase activity of the pigment is cold-inactivated, which tends to support the theory of entropic activation of oxygen consumption (Peat and Soderwall, 1972).

NMR

The evidence is very good that water near interfaces is structured differently from bulk water (Drost-Hansen, 1971, 1972). Probably the most dramatic demonstration was Shereshevsky's (1928) experiment showing very low vapor pressure of the water in capillary tubes. What is still in dispute is whether the particular structure induced by a surface represents an intrinsic "phase" or crystal-like state of water (Drost-Hansen, 1971, 1972), or whether the particular repeating pattern of the surface (such as a macromolecule) imposes its structure onto the water (Ling, 1972). It has been pointed out that enzyme biochemists (the "Pauling School") emphasize the role of ionic side chains of proteins in ordering (or binding) water, while the fiber chemists emphasize the role

of the protein backbone (Ling, 1972). Since estrogen stimulation involves a decrease in protein, DNA, and RNA concentration, because of the great increase in water concentration, the average distance of intra-cellular water from macromolecular surfaces must increase, and this should mean that the water molecules experience fewer restrictions of orientation. High resolution NMR spectra show a distinct broadening of the water line in tissue, relative to bulk water, and less broadening (with a shift upfield) in estrogen-treated uterus than in atrophic uterus from ovariectomized hamsters. Old uteri were not significantly different from young uteri, and both were intermediate between tissue from ovariectomized and estrogen-treated animals. The method, of course, can't determine the quantity of extracellular and intracellular water, unless their movement or shielding is very different, and this apparently is not the case. Diffusion, proton exchange, paramagnetic ions, and lipids are all probable sources of error in this method.

Spin echo NMR can eliminate the possibility that the line broadening results from proton exchange, and shows a slight difference between old and young uteri, as well as between estrogen-treated and untreated young animals, with young uteri showing the greatest difference from bulk water. The old uteri, by being intermediate between younger uteri and bulk water, are somewhat analogous to the malignant tumors in Damadian's study (1971). Even very dense connective tissue (rat knee joint) responds to irritation by a

similar change in water relaxation time, without a large uptake of water (Rokityanskiy and Yakimov, 1971).

Harderian Fluorescence

This strain of hamsters apparently has less active porphyrin secretion from the Harderian glands than do many other rodents, unless their diet is simply richer in B vitamins. A B vitamin (especially pantothenic acid) deficiency is known to cause increased porphyrin secretion by the Harderian glands. Since World War II, animal feeds have become more standardized and are generally supplemented with adequate vitamins, and this may account for the loss of interest in the Harderian glands and their porphyrin secretions. Most (about 80%) barely senescent (14 months) hamsters that have been examined in this lab showed no fluorescence of the eye socket, or only a weak green fluorescence. Beyond this age, however, the typical bright red fluorescence becomes more common. By the time their body weight begins to decrease, which is usually after 15 months, most of the females showed some red fluorescence, but no male did. This is consistent with the observations of Strong (1942) and Figge (1942) regarding the relation of the secretion to estrogen (no males showed fluorescence) and possibly to the likelihood of an animal to develop cancer. Its appearance around the time of reproductive senescence suggests that the liver function may be decreasing at this time, and that the pigment may be

related to the altered uterine metabolism.

Porphyrins are synergistic with estrogen, as well as with carcinogens (Strong, 1942; Figge, et al., 1942; Bittner and Watson, 1946; Kennedy, 1970), and the pyrroles and porphyrins are also conjugated by the liver for excretion via the kidneys. With liver damage, they accumulate, causing porphyria (With, 1968). At least in rodents, concentration of porphyrins in the Harderian glands corresponds to estrogen levels and to the tendency to develop cancer, as well as to deficiencies of the B vitamins essential for liver conjugation (Figge, 1944; Hoffman, 1972).

Uterine Weight, Water Content, and Thickness

Organ weight has been said to be a more sensitive index to metabolic change than any other single condition (Criscuolo, et al., 1955; Rusin, 1971). All dimensions of the hamster uterus that were observed, diameter, thickness of endometrium and myometrium, and total weight, increased with age. Water content of the myometrium decreased with age, but there was no significant difference between young and old endometria's water content.

Though all parts of the old uterus are enlarged, the biggest change with age appears to be the thickness of the myometrium. A large part of the collagen that accumulates with age is in the myometrium (Loeb, 1939).

Estrogen inhibits collagenase (Jeffrey, et al., 1971; Woessner, 1968) and increases collagen synthesis (Henneman, 1968; Kao, et al.,

1964). Loeb (1939) found that estrogen and age both cause collagen accumulation in the uterus. Schaub (1965) found a three-fold increase of uterine collagen in the aged rat, and observed the same age changes (crosslinking) that occur in other tissues.

Finn (1963) found that collagen accumulates in mouse uterus with age, both in a barren uterine horn and in a repeatedly pregnant horn, when the mouse was unilaterally ovariectomized. This weakens the arguments that maintain that collagen formation is largely the result of mechanical stress.

Alkaline phosphatase activity increases with estrogenic stimulation. Therefore, if excessive estrogenic stimulation is responsible for the failure of implantation in senescent animals because of an inadequate level of progesterone, alkaline phosphatase activity should be demonstrable.

In slides prepared by T. J. Connors for a study of enzyme changes in implantation (1969), at all times examined--days 3 1/2, 4, 4 1/2--the epithelium of the senescent uterus was more intensely stained. The senescent stroma was more intensely stained on day 4 1/2, but on day four it was in several cases more lightly stained than in the young.

Since the decidual cell reaction (to an artificial stimulus, viz., the injection of air: Stockton, 1972) is delayed by about twelve hours in the old hamster (and also fails to produce a weight

increase as great as in the young animal), this difference in stromal alkaline phosphatase probably corresponds to that delay. Horikoshi and Wiest (1971), among others, have attributed "uterine refractoriness" to a small progesterone/estrogen ratio.

The epithelial reaction, however, seems to reflect a chronic difference. The senescent myometrium stains nearly as much as the endometrial stroma, but the young myometrium is almost unstained, on all days examined. Again, this suggests a possible chronic difference in degree of "estrogenic" stimulation.

An Organismic Change

These diverse but interlocked observations suggest that a profound reorganization, probably consisting of many compensatory tissue responses to the altered internal environment, occurs during aging. It seems that these changes may be most easily observable in the female mammal, but analogous processes may be practically universal. The mutual adjustment of many parts of a system makes the evaluation of a single component--such as estrogen--very difficult and ambiguous, yet the "meaning" of the configuration to the organism is reasonably consistent and determinate. If the many relevant components of the system can be identified, then it should be possible to evaluate each part without ambiguity. A partial example is the estrogen/progesterone ratio, but it will probably eventually be possible to interpret quantitatively the concentration of other

hormones (especially the salt and sugar regulators), the density and composition of connective tissue, composition of bile pigments, enzymes, etc. For an organismic process, such as aging, it will be appropriate to have precise and quantifiable organismic concepts.

CONCLUSION

Several methods were used to characterize the physiological state of the hamster uterus, with regard to oxygen metabolism, in two age groups, young and senescent. Most of the factors studied were consistent with the concept that the aged uteri are in a relatively "estrogenic" state, but this does not necessarily imply an elevated concentration of steroid estrogens. Factors such as vitamin E deficiency, age pigment deposits, porphyria, ammonia, collagen accumulation, and progesterone deficiency could promote this state, as well as possibly elevated levels of adrenal or ovarian estrogens or other hormones such as catecholamines. In senescent animals oxygen consumption was increased, TTC reduction was high (TTC reduction may simply reflect the oxidative capacity--Cascarano and Zweifach, 1955), catalase was low, peroxidase and uterine pigment were high, and uterine weight was increased considerably. Oxygen tension of the uterine lumen was extremely low in cycling animals of all ages, but was distinctly lower in senescent animals. These changes might be ascribed to a mere vitamin E deficiency, except that the requirement for vitamin E is a function of age. It is possible that vitamin E's "oxygen sparing" effect may be responsible for its effect on reproduction, as it seems to be for its effect in cardiac angina. Considering the anti-fertility effects of small

amounts of exogenous estrogen, it is suggested that this state is responsible for senescent infertility, and it is proposed that luminal oxygen tension may be the crucial factor in both the artificially induced estrogenic sterility and in senescent sterility. Since any irritation promotes estrogen binding by the uterus, the oxygen effect may be even more general. The extraordinarily low oxygen tension recorded in the lumens of both young and senescent ahmsters--apparently lower (especially in the older animals) than any mammalian tissue that has been studied except cancer--suggests that a drastic increase of oxygen tension must be achieved around the time of implantation if the embryos are to survive. A few measurements suggested that this is the case, and a similar change has been reported in other animals, but the closure of the lumen at the time of implantation makes measurements at that time very questionable. If the equivalence of TTC reduction to QO_2 can be accepted, then a study of age differences in TTC reduction by uterine tissues at implantation sites throughout pregnancy would be a very desirable step in confirming this mechanism.

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Ray Peat's Newsletter

"To change something, build a new model that makes the existing model obsolete." --R. Buckminster Fuller

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Hormones, energy, aging, and endogenous carbon monoxide

Our tissues produce carbon monoxide as a normal part of cell breakdown. All kinds of stress that damage tissues increase its formation.

Carbon monoxide increases with aging, and increases stress hormones.

The enzyme which produces carbon monoxide is induced by carbon monoxide.

Carbon monoxide can inhibit the oxidative production of energy, and can increase the rate of non-oxidative, growth supporting energy production.

Carbon monoxide can either stimulate tissue growth or cause atrophy, and can either inhibit or exacerbate inflammation, depending on the surrounding conditions.

Inhibiting its production or accelerating its removal can have therapeutic effects.

In the 1970s, the idea that senescence was a genetically "programmed" function was very popular--a newer form of the doctrine of the essential corruptibility of matter, of Freud's death instinct, and of Hayflick's numerical limit of cells' ability to replicate.

W.D. Denckla's version of programmed aging proposed that the pituitary gland was the agent of this programmed aging. He based his idea on the observation that when animals were kept on a semi-starvation diet, starting before puberty, their puberty was delayed and they lived longer than normal, and on later studies that showed that when animals' pituitary glands were removed before puberty, they lived much longer than normal, and all of their tissues and systems aged at a much slower rate. The implication was that if the gland is present and causes aging, its evolutionary purpose is to cause aging, as well as the other processes such as reproduction.

The particular function that Denckla focused on as an index of aging was oxygen consumption, which decreases by more than 70% between puberty and old age. He showed that the decrease of oxygen consumption was much less when the pituitary gland was removed, if the animal was given the amount of thyroid hormone that it would normally produce. He found some fairly specific pituitary extracts that decreased oxygen consumption, inhibiting the effects of the thyroid hormone, but he never identified a particular pituitary hormone as the antirespiratory aging hormone, or the mechanisms responsible for the extract's effects.

The pituitary's functions are largely directed toward activating glandular tissues, and in doing that it stimulates cell division in the various glands. It's accepted that dividing cells revert to the non-oxidative metabolism, but the mechanism by which the pituitary hormones stimulate cell division isn't generally recognized.

The pituitary hormones, ACTH, FSH, LH, TSH, prolactin, growth hormone, POMC and MSH (melanocyte stimulating hormone) stimulate the production of carbon monoxide in the cells that they stimulate, by activating the enzyme heme oxygenase. This enzyme degrades the heme molecule, which is released from hemoglobin and other proteins in injured tissues, and which in the free state is toxic (Kumar and Bandyopadhyay, 2005). In degrading heme, this enzyme releases free iron atoms and biliverdin, as well as carbon monoxide. Although free iron atoms can cause harmful oxidation, biliverdin, and the bilirubin

that's produced from it, can have beneficial antioxidant effects.

Cells get their energy from the "flow" of electrons from molecules such as sugar and fat, which function as chemical reductants, ultimately to oxygen, which is reduced by them; reduction is the opposite of oxidation, so that's just another way of saying that the fuel molecules are oxidized by oxygen. During cellular stress, such as the release of free heme or free iron, the reducing energy can be misdirected in harmful ways, leading to the cell's death, unless there are molecules, "antioxidants," which can interrupt those processes. Sulfur-containing molecules, in solution (glutathione and other sulfhydryls and disulfides) and sulfur amino acids in the cell's protein structure, are energetically in balance with the flow of energy, from fuel to oxygen, and they act as a buffer or stabilizer of the degree of reduction-oxidation, the redox state. If the sulfur system becomes either too oxidized or too reduced, the cell dies.

Molecules such as vitamin E and vitamin C and bilirubin function as protective antioxidants, but they don't interfere with the oxidations of the crucial respiratory enzyme, cytochrome oxidase. Carbon monoxide has the ability, in certain situations, to function as a protective antioxidant, even while it may be inhibiting the respiratory function, but those situations are very limited. For example, in an atmosphere of 100% oxygen, carbon monoxide protects the lungs from oxygen's otherwise lethal effects, while the high concentration of oxygen protects the respiratory enzyme from complete inhibition by the carbon monoxide. In situations of cell excitation, it can shift the cell's balance toward reduction, by limiting oxidation, creating functional hypoxia

Hypoxia stimulates many cellular reactions, including cell division, in which the cell's structural proteins shift toward a more reduced state of their sulfur atoms. I think it's likely that the antioxidative, antirespiratory, effect of carbon monoxide produced by the enzyme, heme oxygenase, which is activated by the pituitary hormones, is responsible for the activation of cell division in the various glands and other tissues activated by the pituitary.

From the 1930s until the early 1960s, there was considerable interest in the factors that activated or inhibited cell division by shifting the redox balance of the cell toward a more reduced state, for example by using cyanide or pure carbon dioxide to inhibit the respiratory enzyme, or by treating the tissue with glutathione (GSH) or other reduced sulfur compounds. Blocking the respiratory enzyme allows the energy of glycolysis to increase the ratio of NADH to NAD, and the NADH can increase the ratio of reduced glutathione, GSH, to the oxidized disulfide, GSSG.

In the 1950s, Daniel Mazia and Katsuma Dan demonstrated that as cells prepare to divide, with the formation of the mitotic spindle, there is a sudden increase in the reduced sulfur (sulfhydryl, SH) in the cell, and that cell division could be stopped by interfering with the reduction of the sulfur group. Albert Szent-Gyorgyi and Francis Knock believed that the regulation of the sulfur system was a reasonable approach to controlling cancer. Warburg and Szent-Gyorgyi viewed growth and cell division as the basic condition of life, and that cancer was simply a loss of the ability to redirect energy from growth to organization, for which a more oxidized state of the cell was necessary. By the 1970s, it was widely recognized that cancer had a very effective antioxidant protection against destruction by oxidizing agents.

However, in the 1960s, increased interest in the membrane doctrine and DNA research suddenly displaced more traditional types of cell biology and biochemistry. For the membrane doctrine, the material between the genetic substance in the nucleus and the external membrane was a solution of molecules dissolved in water, in which things happened by random diffusion. Learning the Michaelis-Menten equation that describes enzyme actions in a test-tube had the psychological effect of making people assume that random diffusion also governed processes in cells. The coherent chemistry and function of the proteins of the cell, such as could be seen in the mitotic spindle, presented a very different model of the cell. In 1971 the War on Cancer reinforced the molecular genetics approach to understanding cell biology. For the

rest of the century, interactions of the environment with cellular metabolism were of little interest except when they affected the genes and the membranes.

In the last few years there has been a surge of interest in endogenously produced carbon monoxide, probably motivated by the idea that if it's an endogenous substance, it presents opportunities for the pharmaceutical industry. In certain circumstances, its antimetabolic or anti-inflammatory effects can seem protective in ways that could be therapeutically useful, but even those limited benefits have been disputed (Nutter, et al., 1994); the biliverdin and bilirubin produced along with carbon monoxide by heme oxygenase probably account for most of the potentially useful anti-inflammatory effects that have been described. In situations of deadly stress, the ability of increased levels of carbon monoxide to prevent cell death is what makes its involvement in cancer so interesting. The complexity of the balance influenced by carbon monoxide (Wagener, et al., 2003) seems to be routinely ignored.

The phosphorylation system gets most of the attention in studying cell regulatory systems, but some systems that are regulated by phosphorylation are also regulated by the cell's redox state. (Other regulatory systems include pH, the hydration potential, osmolarity, ionic strength, and electrical fields.) An important factor in the regulation of cell functions is a complex of proteins called NF-kappaB, which activates processes of immunity, inflammation, and cell survival. Sulfhydryl reduction is involved in its activation. Ethyl alcohol, which tends to shift the redox balance toward increased NADH and GSH, activates NF-kappaB, and this can be protective for cells in some situations (Ward, et al., 1996), but it's this activation that makes alcohol harmful to the liver, contributing to inflammation, fibrosis and cancer.

Alcohol's liver toxicity is associated with an increased reductive state, higher NADH/NAD, and its toxicity is prevented by agents such as fructose, which protectively lower the NADH/NAD ratio (Khan and O'Brien, 1995, Niknahad, et al., 1995). The reductive activation of iron is an important factor in the toxicity in this case (Khan and O'Brien, 1995). The fact that fructose can protect against cyanide toxicity (Niknahad, et al., 1994), seems likely to be another illustration of the importance of the redox balance.

Increased estrogen can exacerbate liver damage caused by alcohol, by increasing NFkappaB; testosterone has a protective effect, by decreasing NFkappaB (Lee, et al., 2012).

Carbon monoxide activates NF-kappaB, and this is closely related to the ability of cancer cells to avoid the normal dissolution of greatly stressed cells, i.e., to their "immortalization." Cancer's unique antioxidant capacity and its reluctance to undergo the normal apoptotic dissolution when it's unable to participate constructively in normal tissues could be explained by its increased expression of heme oxygenase and its production of carbon monoxide.

Several things in the medical culture divert attention from these associations. First, antioxidants tend to be considered as necessarily benign, including the endogenous antioxidants that are produced in response to stress. Second, estrogen has a special status in the medical culture, and estrogen can not only induce NFkappaB and heme oxygenase, but those can also increase the formation of carbon monoxide. There is a historical reluctance to consider that "antioxidants" and estrogen could be intrinsically involved in degenerative processes, including cancer.

Carbon monoxide has the properties ascribed to Denckla's "death hormone," being increased directly by pituitary hormones (and also by the hormones stimulated by the pituitary), and being able to decrease oxygen consumption. It also seems to cause exactly the changes that Warburg investigated in cancer cells, and attributed to a "respiratory defect." Cancer cells might originate among old cells with a very low metabolic and respiratory rate, but as they develop the properties of cancer they may begin to metabolize at a very high rate (though not necessarily). Their "respiratory defect" is that oxygen is no longer able to inhibit glycolysis, allowing them to consume glucose and amino acids at a continuously high rate. Warburg believed that cancerization was an adaptive survival strategy of cells to escape the

factors interfering with respiration and leading toward atrophy and death.

An enzyme that activates glycolysis, PFKFB4, is normally increased by oxygen deprivation and the hypoxia inducible factor (HIF), but it is also increased by heme oxygenase (Li, et al., 2012). Gluconeogenesis is normally inhibited by heme, which is removed by heme oxygenase. Lactic acid produced by glycolysis activates an enzyme (thioredoxin) that increases cellular sulfhydryl reduction, and increases HIF and also stimulates the formation of new blood vessels by inducing VEGF (Milovanova, et al., 2008), the permeability and growth factor which is essential for the growth of cancer, and which is induced by heme oxygenase. While interfering with the functions of mitochondria, heme oxygenase also stimulates the growth of new mitochondria, along with new blood vessels.

Besides slowing the decrease of oxygen consumption, removing the pituitary gland has also been shown to have beneficial effects on the extracellular material. The presence of the pituitary gland accelerates the aging (thickening, hardening, crosslinking) of collagen in the extracellular matrix, and several factors, including lactic acid and estrogen, contribute to that. Very little effort has been made to investigate the factors involved in extracellular aging, relative to its importance for understanding the aging process and the degenerative diseases. Since oxygen and nutrients reach cells by diffusing through the extracellular matrix, a thickened matrix can contribute to the tissue atrophy from which some cells emerge as cancer cells. Recent studies have confirmed the role of collagen crosslinking in promoting cancer growth and invasiveness (Baker, et al., 2013).

Stresses activate adaptive hormones, especially cortisol, by acting on the hypothalamus to increase CRH, corticotropin release hormone, to activate the pituitary to release ACTH, which activates the adrenals. Carbon monoxide is one of the factors, produced by stress, which activates the secretion of CRH (Navarra, et al., 2001)

Intense exercise increases the production of carbon monoxide temporarily, but regular activity, like calorie restriction (Morgan, et al., 1999; Usuki, et al., 2004; Kang, et al., 2005; Mahlke, et al., 2011), seems to limit its increase with aging.

The level of heme oxygenase increases with aging (Iijima, et al., 1999; Usuki, et al., 2004; Kang, et al., 2005; Hirose, et al., 2003;), reducing the amount of heme available for necessary enzyme functions (Bitar and Shapiro, 1987). The heme synthetic pathway is an energy drain on cells (Atamna, 2004); in breast cancer, for example, which has a high heme oxygenase activity, the heme pathway is 20 times more active than normal (Navone, et al., 1990). Carbon monoxide activates the heme synthetic pathway (by way of erythropoietin), in another potential vicious circle (Cronje, et al., 2004).

The overproduction of heme oxygenase and carbon monoxide in cancer (Al-Owais, et al., 2012) might be dismissed as an effect, rather than a cause, of cancer, except for its role in making cancer cells resistant to natural cell dissolution, apoptosis (Liu, et al., 2004; Banerjee, 2012), chemotherapy (Miyake, et al., 2010), and radiation (Zhang, et al., 2011), and the fact that inhibiting heme oxygenase inhibits cancer growth (Fang, et al., 2012).

Heme oxygenase is induced by all kinds of cancer promoters--viruses (Marinissen, et al., 2006; Martin, et al., 2007), radiation, heavy metals, prostaglandins, estrogen, PUFA, and reactive fragments of fatty acids such as acrolein (a toxic 3-carbon fragment) and HNE (a toxic 9-carbon fragment).

Increasing the activity of heme oxygenase can produce harmful effects, and inhibiting its production can, according to animal studies, produce beneficial effects, for example stopping the growth of cancer, or alleviating seizures (Parfenova, et al., 2004) and symptoms related to liver cirrhosis (Carter, et al., 2002; Tieppo, et al., 2009).

The products of heme oxygenase can cause DNA damage, meeting the conventional requirement for being considered a carcinogen (Ishikawa, 2010), but more plausible metabolic routes to cancer have been suggested (Polo, et al., 1992).

Many experiments with cells and tissues have demonstrated clearly that light causes carbon monoxide to be released from the respiratory

pigment, but there has been little application of this principle to humans. Most of the signs of stress reach their peak in the early morning, following the same diurnal curve as cortisol. In prolonged darkness, great changes in mitochondrial shape and function have been demonstrated. It's likely that at least part of this is caused by carbon monoxide, since its peak formation is in the early morning, and its lowest rate of formation is in the early evening (Levitt, et al., 1994). Blue light and ultraviolet light increase its formation, but orange and red light, which penetrate most deeply into the tissues, can release it from the respiratory pigment.

Several things associated with aging involve some specific effects of heme oxygenase, such as incontinence of the anal and urethral sphincters, malfunction of the esophageal sphincter, loss of tone of the bladder (detrusor) muscle, when the enzyme is increased in those muscles, and reduced curiosity, when the enzyme is increased in the brain. Alzheimer's disease, Parkinson's disease, and schizophrenia all involve increased heme oxygenase in the brain, and in Alzheimer's disease the enzyme is associated with amyloid plaques. These conditions involve some degree of edema in the brain, and the inhibition of heme oxygenase has been found to reduce edema following brain injury (Sharma, et al., 2003). Heme oxygenase increases the leakiness of capillaries (by increasing VEGF), and the presence of heme increases the local production of heme oxygenase. Multiple sclerosis is known to involve disturbance of the capillaries in the brain, and increased heme oxygenase. The frequency of microhemorrhages throughout the body increases with age, along with VEGF and heme oxygenase (Cullen, et al., 2005, 2006). It has been suggested that amyloid is produced as a sealant for the brain's capillaries, compensating for the increased leakiness (Atwood, et al., 2003). The amyloid-beta induces a proteolytic enzyme that degrades the extracellular matrix, increasing the risk of larger hemorrhages (Lee, et al., 2003).

Caffeine, vitamin E, and niacinamide are known to reduce the activity of heme oxygenase. Sodium bicarbonate taken before strenuous exercise reduces the expression of heme oxygenase (Kirk, et al., 2012) and improves endurance. A severe deficiency of vitamin B1 increases the expression of heme oxygenase. Testosterone can restore a youthful balance between heme and heme oxygenase, increasing heme, decreasing heme oxygenase (Bitar and Weiner, 1983). In newborn animals, D-penicillamine (an amino acid that is fairly safe to use as a heavy metal chelator) has lowered heme oxygenase (Oroszlán, et al., 1983). Apigenin, a chemical in guavas and oranges, with anti-inflammatory effects, inhibits heme oxygenase (Abate, et al., 2005). Avoiding exposure to toxic heavy metals, minimizing dietary polyunsaturated fats, and being in brightly lighted environments as much as possible, will help to avoid unnecessary carbon monoxide formation.

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Ray Peat's Newsletter

Events are not the images of dead principles. Robert C. Creegan

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Demystifying dementia: Protective progesterone

There are effective treatments for degenerative nerve diseases, based on well understood biological mechanisms, but they are rarely used, because the relation of those mechanisms to the diseases isn't widely recognized. In recent years, there has been a significant amount of research on the use of progesterone for treating strokes and traumatic brain injury, which involve some of the same biological mechanisms as senile dementia and other brain "diseases." At the same time, though, there have been powerful commercial influences preventing progress in these therapeutic uses.

In the 1970s when I would describe progesterone's effectiveness in PMS, migraines, epilepsy, nephritis, depression, cancer, burns, arthritis, and dementia, it seemed impossible to physicians that a single substance could do those things; they had learned somewhere that "there are no panaceas." I explained some of the reasons for progesterone's "biological generality," but that information had little effect on a medical culture that is organized around the idea that each disease is a certain kind of thing, with its own unique cause or group of causes.

Therapeutic practices are limited by the lack of biological generality underlying the medical understanding of sickness. Hans Selye's concept of stress was part of his search for general biological principles relevant to medicine, but the "stress syndrome," if it has any importance for medicine, is likely to be treated as a thing in itself, rather than as an opportunity for enlarging the understanding of the various "diseases."

Historically, ideas of the causes of disease have changed as new information became available. Tuberculosis and pellagra, which had been thought of as hereditary diseases, came to be seen as infectious and nutritional diseases, as experimental knowledge accumulated. At each stage of understanding, new factual knowledge was used to explain the nature of a disease.

But when the medical industry invested heavily in a certain way of treating a disease, the treatment became a component of how the disease was understood, and tended to freeze a certain way of defining the disease.

In 1847 Rudolph Virchow said "diseases are not isolated phenomena..., not beings that have penetrated into the body..., but they are a certain way in which living beings react to changed circumstances...." In the 20th century, most medical thinking about disease reverted to an earlier essentialist attitude, emphasizing single causes. Cancer was an extreme example of essentialist thinking--it was a "genetically" distinct sort of being, caused by mutant genes, implanted in the victim organism. The treatments all involved removing or killing tissue, and an industry based on those treatments couldn't consider other definitions of the disease.

The same cultural factors are involved in the understanding of functional conditions, including the degenerative brain diseases. When L-DOPA was found to alleviate some of the symptoms of Parkinson's disease, the disease came to be seen as a dopamine deficiency, to the neglect of nearly everything else involved (such as excessive serotoninergic activity--Kaya, et al., 2008) in the degenerative processes. For about 20 years after the drug industry invested in the "cholinergic hypothesis" of Alzheimer's disease, a deficiency of acetylcholine was thought to be an essential feature of the condition, despite a considerable amount of evidence that the theory was unfounded.

Although a disproportionate amount of research was directed by these narrow

pharmaceutical ideas, some basic research continued to be done in universities, but even that was strongly influenced by the cultural and economic situation, the availability of funding and the possibility of publishing. For example, the brain toxic effects of estrogen were usually neglected, and the much higher incidence of Alzheimer's disease in women was usually interpreted as evidence that the disease is caused by a *deficiency* of estrogen. The neurotoxic effects of lipid peroxides and prostaglandins were often ignored, while fish oil was advocated to prevent and treat dementia. The toxic effects of serotonin and nitric oxide were seldom considered, while drugs to increase those were advocated to treat Alzheimer's disease.

These distortions, caused by the economic pressure to make the disease conform to the existing drug business, have prevented the generalization of the understanding and treatment of disease, in line with Virchow's (and Selye's) thinking. If we understand the basic life processes, and the ways in which organisms "react to changed circumstances," then we can look for ways to support more appropriate reactions and to improve the circumstances.

At an early stage of the disease, the brain's glucose consumption rate decreases, and later the blood flow through the brain and the consumption of oxygen decrease. This means that at the beginning of the disease there is a shift from glucose to fatty acids for energy production. This kind of change of fuel occurs during fasting, stress, diabetes, and estrogenic stimulation.

Metabolic energy is fundamental to the development and maintenance of the body, and to the "ways in which living beings react to changed circumstances." It's an obvious first thing to consider when thinking about any "disease," whether it's cancer, radiation sickness, dementia, depression, or traumatic injury.

The well known anatomical features of Alzheimer's disease (neurofibrillary tangles and amyloid plaques) appear as a result of the energy failure, with stress increasing free fatty acids, which inhibit glucose oxidation and promote inflammation and lipid peroxidation, and cause the accumulation of amyloid, which seems to be responsible for the development of the tangles.

The mitochondria are responsible for the efficient production of energy needed for the functioning of complex organisms, and especially for nerves. The enzyme in the mitochondria that reacts directly with oxygen, and that is often rate limiting, is cytochrome c oxidase.

This enzyme is dependent on the thyroid hormone and is inhibited by nitric oxide, carbon monoxide, estrogen, polyunsaturated fatty acids, serotonin, excess or free iron, ionizing radiation, and many toxins, including bacterial endotoxin. Red light, which passes easily through the tissues, reactivates the enzyme, which slowly loses its function during darkness.

Estrogen impairs the mitochondria in multiple ways, including blocking the function of cytochrome oxidase, decreasing the activity of ATP synthase, increasing heme oxygenase which produces carbon monoxide and free iron, damaging mitochondrial DNA, and shifting metabolism from glucose oxidation to fat oxidation, especially by inhibiting the mitochondrial pyruvate dehydrogenase complex. These changes, including the loss of cytochrome oxidase, are seen in the Alzheimer's brain. The fact that this kind of energy impairment can be produced by estrogen doesn't imply that estrogen is the cause, since many other things can cause similar effects--radiation, aluminum, and endotoxin, for example.

But it happens that in the Alzheimer's brain there is an increase of the enzyme aromatase, which synthesizes estrogen. Mice can be genetically modified to lack the aromatase gene, and this kind of mouse was crossed with a mouse that develops a condition similar to Alzheimer's disease. These mice didn't deteriorate mentally as they aged, as related mice with the aromatase gene did, and tests found that no estrogen could be detected in their serum or brain (McAllister, et al., 2010). While the "Alzheimer's" mice with the ability to produce estrogen had 50% less testerosterone than normal, the mutant mice unable to produce estrogen had more testosterone in their brains and serum than either the normal mice or the Alzheimer's mice.

Testosterone has intrinsic cell-protective effects, including opposition to estrogen and cortisol, but in the presence of aromatase, it can be

converted to estrogen. Progesterone has the same basic cell-protective effects, but its metabolites in the brain, the neurosteroids, are specific neuroprotectors. DHEA also has brain-protective effects.

All of these cell-protective steroids have a negative feedback relation to the luteinizing hormone, LH, that is, as they are increased by its action, they inhibit the secretion of LH. Estrogen has a positive feedback relation to the gonadotropins, meaning that a little estrogen can stimulate an increase of LH and FSH, leading to greater production of estrogen. This means that a deficiency of progesterone, relative to estrogen, will tend to cause increased LH, unless other factors change. Both FSH and LH are generally increased at menopause and in Alzheimer's disease. LH increases about 3 to 4-fold in both men and women with aging (Casadesus, et al., 2006), but it increases more (in both the brain and serum) in Alzheimer's disease.

The increased LH in Alzheimer's disease (rather than the low ratio of progesterone to estrogen) is being discussed as a basic cause of Alzheimer's disease. A drug that lowers LH (leuprolide) decreases the formation of amyloid and improves cognitive functions in mice, and it has been suggested that the use of leuprolide in prostate cancer patients might account for their lower incidence of degenerative nervous diseases. LH is present in increased amounts in both the serum and nerves of Alzheimer's patients, and in vitro, it increases the formation of amyloid (Meethal, et al., 2005). Transgenic mice that produce increased amounts of LH perform poorly in maze tests, but similar mice that lack the LH receptor perform normally (Casadesus, et al., 2007).

LH, like other pituitary hormones, has a variety of pro-inflammatory effects, for example in rheumatoid arthritis and lung inflammation. DHEA and testosterone can reduce inflammation and lower LH, but both of those can be converted to estrogen by aromatase. Progesterone, however, has a very broad spectrum of antiinflammatory actions, including the inhibition of LH, and its metabolites (the "neurosteroids) also have various protective effects in the brain. One of the metabolites is able to inactivate the aromatase enzyme (Pasqualini and Chetrite, 2008). Although they are called neurosteroids, they are also protective against cancer and are an important part of the progestational system in pregnancy.

Progesterone's antiinflammatory effects include the inhibition of the enzymes that form prostaglandins, overlapping with aspirin in that function. However, unlike aspirin, progesterone also activates an enzyme that degrades prostaglandins. Besides being important amplifiers of inflammatory reactions, the prostaglandins inhibit mitochondrial energy production (Cherkasskaia, et al., 1982) and activate aromatase and estrogen synthesis. Estrogen activates the formation of prostaglandins (Toda, et al., 2012) and inhibits the enzyme that degrades them (Chang and Tai, 1985). Progesterone also inhibits the synthesis of nitric oxide (Wang, et al., 2012); its inhibition of nitric oxide protects mitochondrial respiration (Deniselle, et al., 2012). Since estrogen increases the production of prostaglandins and nitric oxide, and decreases the degradation of prostaglandins, progesterone's various estrogen-inhibiting actions are a very important part of its protective effects.

More than 40 years ago D.G. Stein started studying brain injury in animals and the possibility of preventing or reducing its long range effects. For more than 20 years he didn't find anything that helped, but in 1992 a student, Robin Roof, did experiments showing that progesterone injections reduced or prevented brain edema after a brain contusion. Pseudopregnancy, in which there is a high ratio of progesterone to estrogen, also prevented brain edema. An oxidative breakdown product of arachidonic acid, isoprostane, associated with dementia was reduced by 2/3 in the animals treated with progesterone (Roof, et al., 1997). In 2000 and 2001, both Roof and Stein published some articles suggesting that estrogen might also be beneficial, but after the 2002 WHI announcement that estrogen increased dementia, I haven't seen any more estrogen publications from either of them. Referring later to the early studies, Roof said she "didn't look at estrogen during that time because it did not seem to be neuroprotective in that model (at least in terms of edema)."

Brain edema, which is an early response to any brain injury, is seldom discussed as a feature

of Alzheimer's dementia, but MRI studies clearly show that brain water is disproportionately intracellular, meaning that the cells are swollen. A protein called "aquaporin-4" is associated with brain injury and edema, and it is increased by estrogen, and decreased by progesterone.

Progesterone's very large effect on oxidative damage in the animal studies was very important, because the isoprostanes and prostaglandins are now known to be closely associated with Alzheimer's disease and other age related neurodegenerative diseases. The spontaneously formed isoprostanes were discovered in 1992, and it was several years before their role in degenerative diseases began to be studied.

Other new knowledge of the ways in which polyunsaturated fats break down has become available in this same period. For example, acrolein, which is elevated in Alzheimer's disease, is from 10 to 100 times more reactive than some of the better known oxidative fragments, and it is formed mainly from omega-3 polyunsatured fatty acids, especially DHA and EPA. It inhibits respiration in brain mitochondria, damages proteins, forming "advanced glycation end-products" (Pietkiewicz, et al., 2011), and is toxic to brain cells. It inhibits the uptake of glutamate (Lovell, et al., 2000) which would contribute to excitotoxity to nerve cells. (Polyunsaturated fatty acids and estrogen tend to promote excitotoxity in other ways, too.)

Acrolein's self-stimulating production from DHA is another factor that could account for the predominance of Alzheimer's disease in women, since, under the influence of estrogen, women accumulate significantly more DHA than men (Giltay, et al., 2004), and similar effects can be seen in animal studies (McNamara, et al., 2008).

This is probably related to the increased vitamin E requirement caused by estrogen (Briggs, 1975), and to the ability of estrogen to increase the age pigment, lipofuscin (Harris, 1966; Graham, 1968; MÃ¼ntzing and Nilsson, 1972; Karkare, et al., 1995). The shorter chain fatty acids of coconut oil are more easily oxidized for energy than long chain fatty acids, and their saturation makes them resistant to the random oxidation produced by inflammation, so they don't support the production of acrolein or age pigment; along with their reported antiinflammatory effects, these properties might be responsible for their beneficial effects that have been seen in Alxheimer's disease.

The myelin content is decreased in Alzheimer's disease, and progesterone is known to stimulate its resynthesis by the oligodendrocytes; the neurosteroids are known to be involved in the regeneration, survival, and function of brain cells (Schumacher, et al., 1996). Cholesterol, which is the precursor for pregnenolone, progesterone, and DHEA, is lost from the white matter in Alzheimer's disease (Roher, et al, 2002), and replacing cholesterol in the brain can have protective effects against the deposition of amyloid (Sponne, et al., 2004). Thyroid hormone is involved in the synthesis of the neurosteroids, the repair of myelin, and all the essential brain functions, as well as systemic regulation of hormones.

Although the growth hormone is one of the hormones increased by stress and estrogens which produce free fatty acids by lipolysis, it's generally assumed that it decreases in Alzheimer's disease, as it does in normal aging. However, it's known that somatostatin, the inhibitor of growth hormone secretion, is decreased (by about 50%) in Alzheimer's disease. Normal people have very low serum growth hormone in the morning, but Alzheimer patients' growth hormone is high in the morning. Somatostatin is inhibited by estrogen and serotonin, which are both increased in Alzheimer's disease, and hypothyroidism could also contribute to the lack of somatostatin (Baldini, et al., 1992). The deficiency of somatostatin probably contributes to the increased TSH as well as growth hormone found in Alzheimer's disease (Christie, et al., 1987). Decreased T3, the active thyroid hormone, in the Alzheimer's brain is another factor in the elevated TSH.

Other lipolytic hormones that are increased in Alzheimer's disease and other neurodegenerative diseases include ACTH, cortisol, and adrenalin. Growth hormone stimulates the release of serotonin (and reduces dopamine), and serotonin in turn stimulates growth hormone release.

The maladaptive sequence, starting from stress or hypothyroidism, would typically involve increased absorption of endotoxin, leading to interference with mitochondrial respiration, a shift to fat oxidation, inflammation, and the increase of a wide range of stress hormones. Each of these steps happens to interfere with the production of progesterone, leading to increased LH.

Even a seemingly minor brain trauma can start a process that leads to permanent and progressive impairment. A brain injury increases the likelihood of later developing Alzheimer's disease or Parkinson's disease. A mild concussion, or exposure to ionizing radiation, or even chronic exposure to "weak" electromagnetic fields, can activate these same mechanisms of inflammation and deterioration. These after-effects involve the same mechanisms as the radiation bystander effects--a spreading of inflammatory processes and edema. Strokes, tumors, and infections also typically activate the same processes of inflammation and swelling.

Although just supplementing with progesterone and/or thyroid can sometimes produce rapid improvement in brain function, it would be reasonable to correct as many of the metabolic defects as possible, starting with the elimination of polyunsaturated fats from the diet, and eating an antiinflammatory diet, low in iron, phosphate, antithyroid or estrogenic substances, and starches, with fruits and saturated fats as the main calorie sources. Aspirin, vitamin K (essential for brain lipid synthesis and growth regulation), magnesium, niacinamide, caffein, antihistamines and antiserotonin drugs (such as cyproheptadine), antibiotics (especially antiinflammatory antibiotics such as minocycline) and diuretics such as acetazolamide are supplements that are likely to be beneficial. Vitamin D should be measured, because a deficiency can impair brain functions. (The correct blood test for vitamin D status is 25(OH)vitamin D, not 1,25 dihydroxyvitamin D.) Small amounts of baking soda, or rebreathing in a bag to increase carbon dioxide, can increase blood circulation to the brain.

Getting a generous amount of light on the head has beneficial effects on mental functions, by increasing the activity of cytochrome oxidase (Rojas, et al., 2012) and reducing inflammation. Cytochrome oxidase in the brain can also be increased by mental stimulation, learning, and moderate exercise, but excessive exercise or the wrong kind of exercise ("eccentric") can lower it (Aguiar, et al., 2007, 2008), probably by increasing the stress hormones and free fatty acids. Sedentary living at high altitude has beneficial effects on mitochondria similar to moderate exercise at sea level (He, et al., 2012).

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Ray Peat's Newsletter

If the world were good for nothing else, it is a fine subject for speculation. **William Hazlitt**

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Phosphate, activation, and aging

Recent publications are showing that excess phosphate can increase inflammation, tissue atrophy, calcification of blood vessels, cancer, dementia, and, in general, the processes of aging. This is especially important, because of the increasing use of phosphates as food additives.

Previously, the complications of chronic kidney disease, with increased serum phosphate, were considered to be specific for that condition, but the discovery of a phosphate-regulating gene named klotho (after one of the Fates in Greek mythology) has caused a lot of rethinking of the biological role of phosphate. In the 19th century, phosphorus was commonly called brain food, and since about 1970, its involvement in cell regulation has become a focus of reductionist thinking. ATP, adenosine triphosphate, is seen as the energy source that drives cell movement as well as the "pumps" that maintain the living state, and as the source of the cyclic AMP that is a general activator of cells, and as the donor of the phosphate group that activates a great number of proteins in the "phosphorylation cascade." When tissues calcified in the process of aging, calcium was blamed (ignoring the existence of calcium phosphate crystals in the tissues), and low calcium diets were recommended. Recently, when calcium supplements haven't produced the intended effects, calcium was blamed, disregarding the other materials present in the supplements, such as citrate, phosphate, orotate, aspartate, and lactate.

I have a different perspective on the "phosphorylation cascade," and on the other functions of phosphate in cells, based largely on my view of the role of water in cell physiology. In the popular view, a stimulus causes a change of shape in a receptor protein, causing it to become an active enzyme, catalyzing the transfer of a phosphate group from ATP to another protein, causing it to change shape and become activated, and to transfer phosphate groups to other molecules, or to remove phosphates from active enzymes, in chain reactions. This is standard biochemistry, that can be done in a test tube.

Starting around 1970, when the involvement of phosphorylation in the activation of enzymes in glycogen breakdown was already well known, people began noticing that the glycogen phosphorylase enzyme became active immediately when the muscle cell contracted, and that phosphorylation followed the activation. Phosphorylation was involved in activation of the enzyme, but if something else first activated the enzyme (by changing its shape), the addition of the phosphate group couldn't be considered as causal, in the usual reductionist sense. It was one participant in a complex causal process. I saw this as a possible example of the effect of changing water structure on protein structure and function. This view of water questions the relevance of test tube biochemistry.

Enzymes are known which suddenly become inactive when the temperature is lowered beyond a certain point. This is because soluble proteins arrange their shape so that their hydrophobic regions, the parts with fat-like side-chains on the amino acids, are inside, with the parts of the chain with water-soluble amino acids arranged to be on the outside, in contact with the water. The "wetness" of water, its activity that tends to exclude the oily parts of the protein molecule, decreases as the temperature decreases, and some proteins are destabilized when the relatively hydrophobic group is no longer repelled by the surrounding cooler water.

In the living cell, the water is all within a very short distance of a surface of fats or fat-like

proteins. In a series of experiments, starting in the 1960s, Walter Drost-Hansen showed that, regardless of the nature of the material, the water near a surface is structurally modified, becoming less dense, more voluminous. This water is more "lipophilic," adapting itself to the presence of fatty material, as if it were colder. This change in the water's properties also affects the solubility of ions, increasing the solubility of potassium, decreasing that of sodium, magnesium, and calcium (Wiggins, 1973).

When a muscle contracts, its volume momentarily decreases (Abbott and Baskin, 1962). Under extremely high pressure, muscles contract. In both situations, the work-producing process of contraction is associated with a slight reduction in volume. During contraction of a muscle or nerve, heat is given off, causing the temperature to rise. During relaxation, recovering from excitation, heat is absorbed (Curtin and Woledge, 1974; Westphal, et al., 1999; Constable, et al. 1997). In the case of a nerve, following the heating produced by excitation, the temperature of the nerve decreases below the starting temperature (Abbot, et al., 1965). Stretching a muscle causes energy to be absorbed (Constable, et al., 1997). Energy changes such as these, without associated chemical changes, have led some investigators to conclude that muscle tension generation is "entropy driven" (Davis and Rodgers, 1995).

Kelvin's description (1858) of the physics of water in a soap bubble, "...if a film such as a soap-bubble be enlarged . . . it experiences a cooling effect . . . ," describes the behavior of nerves and muscles, absorbing energy or heat when they are relaxing (or elongating), releasing it when they are excited/contracting.

Several groups of experimenters over the last 60 years have tried to discover what happens to the missing heat; some have suggested electrical or osmotic storage, and some have demonstrated that stretching generates ATP, arguing for chemical storage. Physical storage in the form of structural changes in the water-protein-lipid system, interacting with chemical changes such as ATP synthesis, have hardly been investigated.

Early studies of muscle chemistry and contraction found that adding ATP to a viscous solution of proteins extracted from muscle reduced its viscosity, and also that the loss of ATP from muscle caused its hardening, as in rigor mortis; if the pH wasn't too acidic, the dead muscle would contract as the ATP content decreased. Szent-Gyorgyi found that a muscle hardened by rigor mortis became soft again when ATP was added.

Rigor mortis is an extreme state of fatigue, or energy depletion. Early muscle studies described the phenomenon of "fatigue contracture," in which the muscle, when it reaches the point at which it stops responding to stimulation, is maximally contracted (this has also been called delayed relaxation). Ischemic contracture, in the absence of blood circulation, occurs when the muscle's glycogen is depleted, so that ATP can no longer be produced anaerobically (Kingsley, et al., 1991). The delayed relaxation of hypothyroid muscle is another situation in which it is clear that ATP is required for relaxation. (In the Achilles tendon reflex test, the relaxation rate is visibly slowed in hypothyroidism.) A delayed T wave in the electrocardiogram, and the diastolic contracture of the failing heart show the same process of delayed relaxation. Supplementing the active thyroid hormone, T3, can quickly restore the normal rate of relaxation, and its beneficial effects have been demonstrated in heart failure (Pingitore, et al., 2008; Wang, et al., 2006; Pantos, et al., 2007; Galli, et al., 2008).

A large part of the magnesium in cells is bound to ATP, and the magnesium-ATP complex is a factor in muscle relaxation. A deficiency of either ATP or magnesium contributes to muscle cramping. When a cell is stimulated, causing ATP to release inorganic phosphate, it also releases magnesium. Above the pH of 6.7, phosphate is doubly ionized, in which state it has the same kind of structural effect on water that magnesium, calcium, and sodium have, causing water molecules to be powerfully attracted to the concentrated electrical charge of the ion. Increasing the free phosphate and magnesium opposes the effect of the surfaces of fats and proteins on the water structure, and tends to decrease the solubility of potassium in the water, and to increase the water's "lipophobic" tendency to minimize its contacts with fats and the fat-like surface of

proteins, causing the proteins to rearrange themselves.

These observations relating to the interactions of water, solutes and proteins in muscles and nerves provide a coherent context for understanding contraction and conduction, which is lacking in the familiar descriptions based on membranes, pumps, and cross-bridges, but I think they also provide a uniquely useful context for understanding the possible dangers of an excess of free phosphate in the body.

A few people (M. Thomson, J. Gunawardena, A.K. Manrai) are showing that principles of mass-action help to simplify understanding the networks of phosphorylation and dephosphorylation that are involved in cell control. But independently from the phosphorylation of proteins, the presence of phosphate ion in cell water modifies the cell's ion selectivity, shifting the balance toward increased uptake of sodium and calcium, decreasing potassium, tending to depolarize and "activate" the cell.

About 99% of the publications discussing the mechanism of muscle contraction fail to mention the presence of water, and there's a similar neglect of water in discussions of the energy producing processes in the mitochondrion. The failure of mitochondrial energy production leads to lipid peroxidation, activation of inflammatory processes, and can cause disintegration of the energy producing structure. Increased phosphate decreases mitochondrial energy production (Duan and Karmazyn, 1989), causes lipid peroxidation (Kowaltowski, et al., 1996), and activates inflammation, increasing the processes of tissue atrophy, fibrosis, and cancer.

For about twenty years it has been clear that the metabolic problems that cause calcium to be lost from bones cause calcium to increase in the soft tissues, such as blood vessels. The role of phosphate in forming calcium phosphate crystals had until recently been assumed to be passive, but some specific "mechanistic" effects have been identified. For example, increased phosphate increases the inflammatory cytokine, osteopontin (Fatherazi, et al., 2009), which in bone is known to activate the process of decalcification, and in arteries is involved in calcification processes (Tousoulis, et al., 2012). In the kidneys, phosphate promotes calcification (Bois and Selye, 1956), and osteopontin, by its activation of inflammatory T-cells, is involved in the development of glomerulonephritis, as well as in inflammatory skin reactions (Yu, et al., 1998). High dietary phosphate increases serum osteopontin, as well as serum phosphate and parathyroid hormone, and increases the formation of tumors in skin (Camalier, et al., 2010). Besides the activation of cells and cell systems, phosphate (like other ions with a high ratio of charge to size, including citrate) can activate viruses (Yamanaka, et al., 1995; Gouvea, et al., 2006). Aromatase, the enzyme that synthesizes estrogen, is an enzyme that's sensitive to the concentration of phosphate (Bellino and Holben, 1989).

More generally, increased dietary phosphate increases the activity of an important regulatory enzyme, protein kinase B, which promotes organ growth. A high phosphate diet increases the growth of liver (Xu, et al., 2008) and lung (Jin, et al., 2007), and promotes the growth of lung cancer (Jin, et al., 2009). An extreme reduction of phosphate in the diet wouldn't be appropriate, however, because a phosphate deficiency stimulates cells to increase the phosphate transporter, increasing the cellular uptake of phosphate, with an effect similar to the dietary excess of phosphate, i.e., promotion of lung cancer (Xu, et al., 2010). The optimum dietary amount of phosphate, and its balance with other minerals, hasn't been determined.

While increased phosphate slows mitochondrial energy production, decreasing its intracellular concentration increases the respiratory rate and the efficiency of ATP formation. A "deficiency" of polyunsaturated fatty acids has this effect (Nogueira, et al., 2001), but so does the consumption of fructose (Green, et al., 1993; Lu, et al., 1994).

In a 1938 experiment (Brown, et al.) that intended to show the essentiality of unsaturated fats, a man, William Brown, lived for six months on a 2500 calorie diet consisting of sucrose syrup, a gallon of milk (some of it in the form of cottage cheese), and the juice of half an orange, besides some vitamins and minerals. The experimenters remarked about the surprising disappearance of

the normal fatigue after a day's work, as well as the normalization of his high blood pressure and high cholesterol, and the permanent disappearance of his frequent life-long migraine headaches. His respiratory quotient increased (producing more carbon dioxide), as well as his rate of resting metabolism. I think the most interesting part of the experiment was that his blood phosphate decreased. In two measurements during the experimental diet, his fasting plasma inorganic phosphorus was 3.43 and 2.64 mg. per 100 ml. of plasma, and six months after he had returned to a normal diet the number was 4.2 mg/100 ml. Both the deficiency of the "essential" unsaturated fatty acids, and the high sucrose intake probably contributed to lowering the phosphate.

In 2000, researchers who were convinced that fructose is harmful to the health, reasoned that its harmful effects would be exacerbated by consuming it in combination with a diet deficient in magnesium. Eleven men consumed, for six months, test diets with high fructose corn syrup or starch, along with some fairly normal U.S. foods, and with either extremely low magnesium content, or with slightly deficient magnesium content. The authors' conclusion was clearly stated in the title of their article, that the combination adversely affects the mineral balance of the body.

However, looking at their results in the context of these other studies of the effects of fructose on phosphate, I don't think their conclusion is correct. Even on the extremely low magnesium intake, both their magnesium and calcium balances were positive, meaning that on average their bodies accumulated a little magnesium and calcium, even though men aged 22 to 40 presumably weren't growing very much. To steadily accumulate both calcium and magnesium, with the calcium retention much larger than the magnesium, the minerals were probably mostly being incorporated into their bones. Their phosphate balance, however, was slightly negative on the "high fructose" diet. If the sugar was having the same effect that it had on William Brown in 1938 (and in animal experiments), some of the phosphate loss was accounted for by the reduced amount in blood and other body fluids, but to continue through the months of the experiment, some of it must have represented a change in the composition of the bones. When there is more carbon dioxide in the body fluids, calcium carbonate can be deposited in the bones (Messier, et al., 1979). Increased carbon dioxide could account for a prolonged negative phosphate balance, by taking its place in the bones in combination with calcium and magnesium.

Another important effect of carbon dioxide is in the regulation of both calcium and phosphate, by increasing the absorption and retention of calcium (Canzanello, et al., 1995), and by increasing the excretion of phosphate. Increased carbon dioxide (as dissolved gas) and bicarbonate (as sodium bicarbonate) both increase the excretion of phosphate in the urine, even in the absence of the parathyroid hormone. Below the normal level of serum bicarbonate, reabsorption of phosphate by the kidneys is greatly increased (Jehle, et al., 1999). Acetazolamide increases the body's retention of carbon dioxide, and increases the amount of phosphate excreted in the urine.

Much of the calcium dissolved in the blood is in the form of a complex of calcium and bicarbonate, with a single positive charge (Hughes, et al., 1984). Failure to consider this complexed form of calcium leads to errors in measuring the amount of calcium in the blood, and in interpreting its physiological effects, including its intracellular behavior. Hyperventilation can cause cramping of skeletal muscles, constriction of blood vessels, and excitation of platelets and other cells; the removal of carbon dioxide from the blood lowers the carbonic acid, changing the state and function of calcium. Hyperventilation increases phosphate and parathyroid hormone, and decreases calcium (Krapf, et al., 1992).

Since estrogen tends to cause hyperventilation, lowering carbon dioxide, its role in phosphate metabolism should be investigated more thoroughly. Work by Han, et al. (2002) and Xu, et al. (2003) showed that estrogen increases phosphate reabsorption by the kidney, but estrogen also increases cortisol, which decreases reabsorption, so the role of estrogen in the whole system has to be be considered.

This calcium solubilizing effect of bicarbonate, combined with its phosphaturic effect, probably accounts for the relaxing effect of carbon dioxide

on the blood vessels and bronchial smooth muscles, and for the prevention of vascular calcification by the thyroid hormones (Sato, et al., 2005, Tatar, 2009, Kim, et al., 2012). Distensibility of the blood vessels and heart, increased by carbon dioxide, is decreased in hypothyroidism, heart failure, and by phosphate.

While fructose lowers intracellular phosphate, it also lowers the amount that the intestine absorbs from food (Kirchner, et al.,2008), and the Milne-Nielsen study suggests that it increases phosphate loss through the kidneys. The "anti-aging" protein, klotho, increases the ability of the kidneys to excrete phosphate (Dërmaku-Sopjani, et al., 2011), and like fructose, it supports energy production and maintains thermogenesis (Mori, et al., 2000).

Lowering the amount of phosphate in the blood allows the parathyroid hormone to decrease. While the parathyroid hormone also prevents phosphate reabsorption by the kidneys, it causes mast cells to release serotonin (and serotonin increases the kidneys' reabsorption of phosphate), and possibly has other pro-inflammatory effects. For example, deleting the PTH gene compensates for the harmful (accelerated calcification and osteoporosis) effects of deleting the klotho gene, apparently by preventing the increase of osteopontin (Yuan, et al., 2012).

Niacinamide is another nutrient that lowers serum phosphate (Cheng, et al., 2008), by inhibiting intestinal absorption (Katai, et al., 1989), and also by reducing its reabsorption by the kidneys (Campbell, et al., 1989). Niacinamide's reduction of free fatty acids by inhibiting lipolysis, protecting the use of glucose for energy, might be involved in its effect on phosphate (by analogy with the phosphate lowering action of a deficiency of polyunsaturated fatty acids). Aspirin is another antilipolytic substance (de Zentella, et al., 2002) which stimulates energy production from sugar and lowers phosphate, possibly combined with improved magnesium retention (Yamada and Morohashi, 1986).

A diet that provides enough calcium to limit activity of the parathyroid glands, and that is low in phosphate and polyunsaturated fats, with sugar rather than starch as the main carbohydrate, possibly supplemented by niacinamide and aspirin, should help to avoid some of the degenerative processes associated with high phosphate: fatigue, heart failure, movement discoordination, hypogonadism, infertility, vascular calcification, emphysema, cancer, osteoporosis, and atrophy of skin, skeletal muscle, intestine, thymus, and spleen (Ohnishi and Razzaque, 2010; Shiraki-Iida, et al., 2000; Kuro-o, et al., 1997; Osuka and Razzaque, 2012). The foods naturally highest in phosphate, relative to calcium, are cereals, legumes, meats, and fish. Many prepared foods contain added phosphate. Foods with a higher, safer ratio of calcium to phosphate are leaves, such as kale, turnip greens, and beet greens, and many fruits, milk, and cheese. Coffee, besides being a good source of magnesium, is probably helpful for lowering phosphate, by its antagonism to adenosine (Coulson, et al., 1991).

Although increased phosphate generally causes vascular calcification (increasing rigidity, with increased systolic blood pressure), when a high level of dietary phosphate comes from milk and cheese, it is epidemiologically associated with reduced blood pressure (Takeda, et al., 2012).

Phosphate toxicity offers some interesting insights into stress and aging, helping to explain the protective effects of carbon dioxide, thyroid hormone, sugar, niacinamide, and calcium. It also suggests that other natural substances used as food additives should be investigated more thoroughly. Excessive citric acid, for example, might activate dormant cancer cells (Havard, et al., 2011), and has been associated with malignancy (Blüml, et al., 2011). Nutritional research has hardly begun to investigate the optimal ratios of minerals, fats, amino acids, and other things in foods, and how they interact with the natural toxicants, antinutrients, and hormone disrupters in many organisms used for food.

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Ray Peat's Newsletter

"Medicine is a social science, and politics is nothing else but medicine on a large scale." **Rudolph Virchow c. 1848**

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Hot flashes, energy, and aging

Around the time that menstruation and fertility are ending, certain biological problems are more likely to occur. Between the ages of 50 and 55, about 60% of women experience repeated episodes of flushing and sweating. Asthma, migraine, epilepsy, arthritis, varicose veins, aneurysms, urticaria, reduced lung function, hypertension, strokes, and interstitial colitis are some of the other problems that often begin or get worse at the menopause, but that normally aren't considered to be causally related to it.

Recently, hot flashes are being taken more seriously, because of their association with increased inflammation, heart disease, and risk of dementia. Around the same age, late 40s to mid-50s, men begin to have a sudden increase of some of the same health problems, including night sweats, anxiety, and insomnia. In both sexes, the high incidence of depression in this age group has usually been explained "psychologically," rather than biologically.

When the estrogen industry began concentrating on women of menopausal age (after the disastrous years of selling it as a fertility drug), "estrogen replacement" therapy was promoted as a cure for the problems associated with menopause, including hot flashes, which were explained as the result of a deficiency of estrogen. However, in recent years, the phrase "estrogen deficiency" has begun to be replaced by the phrase "estrogen withdrawal," because it has been found that women with hot flashes don't necessarily have less estrogen in their blood stream than women who don't have hot flashes.

Associated with this change of terminology, there has been a recognition that changes in the temperature regulating system in the brain, rather than changes in the amount of estrogen, are responsible for the hot flashes, but mainstream medicine has carefully avoided the investigation of this subject. The effects of estrogen on the thermoregulatory system are very clear, but the standard medical view is that the physiology of hot flashes simply isn't understood.

Since the medical literature boldly describes the mechanisms of the circulatory system and the causes of major problems such as heart attacks, high blood pressure, and strokes, it's odd that it doesn't have an explanation for "hot flashes."

But looking at this historically, I think this selective ignorance is necessary, for the protection of some doctrines that have become very important for conventional medicine.

When doctors are talking about diseases of the heart and circulatory system, it's common for them to say that estrogen is protective, because it causes blood vessels to relax and dilate, improving circulation and preventing hypertension. The fact that estrogen increases the formation of nitric oxide, a vasodilator, is often mentioned as one of its beneficial effects. But in the case of hot flashes, dilation of the blood vessels is exactly the problem, and estrogen is commonly prescribed to *prevent* the episodic dilation of blood vessels that constitutes the hot flash. Nitric oxide increases in women in association with the menopause (Watanabe, et al., 2000), and it is increased by inflammation, and hot flushes are associated with various mediators of inflammation, but, as far as I can tell, no one has measured the production of nitric oxide during a hot flash. Inhibitors of nitric oxide formation reduce vasodilation during hot flushes (Hubing, et al., 2010).

Starting in the 1940s, the doctrine that menopause is the result of changes in the ovaries, involving a depletion of eggs and an associated

loss of estrogen production, was widely taught to medical students. By the 1970s, the taboo against discussing menopause publicly was fading, and the mass media began teaching the public that hot flashes are the result of an estrogen deficiency, and that "estrogen replacement" is the most appropriate and effective treatment, and in the next 20 years **almost half the women in the US began taking it around the time of menopause.** This practice became routine at a time when "evidence based medicine" was being promoted as a new standard, but there was no evidence that women experiencing hot flashes were deficient in estrogen (in fact, there was evidence that they weren't), and there was evidence that hot flashes began when the first menstrual period was missed, which coincided with, and resulted from, a failure to produce a functional corpus luteum, preventing the production of a normal amount of progesterone. But the silly old doctrine of deficiency is often restated by professors, as if there was no doubt about it (for example, Rance, 2009; Bhattacharya and Keating, 2012).

This extremely persistent disregard for important evidence about the nature of menopause and its symptoms was guided by the estrogen industry, which began in the 1930s to call estrogen "the female hormone," disregarding the facts about the biological roles of estrogen and progesterone, because chemicals with estrogenic effects were numerous and cheap, while progesterone was expensive, and had no synthetic equivalents. At the time the pharmaceutical industry began promoting estrogen as the female hormone to prevent miscarriage, it was already well known that it could produce abortion, as well as causing inflammation and cancer, and some of the most famous estrogen researchers were warning of its multiple dangers in the 1930s.

Menopause is a major landmark of aging, and if its meaning is radically misunderstood, a coherent understanding of aging is unlikely, and without an understanding of the loss of functions with age, we won't really understand life. More specifically, the real causes of the many serious problems occurring in association with the menopause will be ignored. Finding the causes of the seemingly trivial hot flash will affect the way we understand aging and its diseases.

If a common occurrence is thought to have some importance in itself, or to relate closely to something of importance, it will be described carefully, and its general features will become part of the common understanding. It's clear that our medical culture hasn't considered the hot flash to be important, because there are still physicians who believe that the hot flash represents a rise of body temperature caused by a sudden increase of heat production, which they sometimes explain as an upward fluctuation of thyroid gland activity. Measurement of body temperature before and during hot flashes has shown clearly that the internal temperature is lowered slightly by the hot flash, as heat is lost from the skin, as a result of vasodilation. Physiologists have been studying the differences in temperature regulation between men and women, and the effects of hormones on temperature regulation, for more than 70 years, but the medical profession in the United States showed almost no interest in the subject for about 50 years.

August Weismann's doctrine of "mortal soma, immortal germ line," led people to postulate that "primordial germ" cells migrated into the ovary (consisting of "somatic" cells) during embryonic development, and that the baby was born with a supply of germ cells that was used up during the reproductive lifetime, accounting for the decline of fertility with aging. The fact that menstrual cycles ended around the time that fertility ended was explained by the idea that ovulation caused the release of estrogen, and that the absence of eggs caused a failure to produce estrogen, and that the absence of estrogen led to the failure of the cyclical uterine changes. It was all deduced from a mistaken ideology about the nature of life.

Cancer of the endometrium (lining) of the uterus and breast cancer were known to be the first and second cancers, respectively, produced by uninterrupted exposure to estrogen (for example, Lipshutz, 1950). Investigation of the causes of endometrial cancer showed that women with anovulatory cycles, that failed to produce progesterone, or who had a reduced production of progesterone, developed overgrowth of the

endometrium, and that these were the women who were later most likely to develop cancer of the endometrium. The peak incidence of endometrial cancer is in the postmenopausal years, resulting from prolonged exposure to estrogen, unopposed by progesterone. The medical belief* that "ovulation produces estrogen," and that the absence of menstruation means an absence of estrogen, has been very harmful to women's health.

Several laboratories, from the 1950s through the 1980s, investigated the causes of age-related infertility. A.L. Soderwall, among others, demonstrated that an excess of estrogen makes it impossible for the uterus to maintain a pregnancy. Subsequently, his lab showed that neither changes in the eggs nor changes in the uterus could explain age related infertility. Altered pituitary hormone cycles, resulting from changes in the brain, could account for the major changes in the ovaries and uterus.

Other experimenters, including P.M. Wise, V.M. Sopelak and R.L. Butcher (1982), P. Ascheim (1983), and D.C. Desjardins (1995) have clarified the interactions between the ovaries and the brain. For example, when the ovaries of an old animal are transplanted into a young animal, they are able to function in response to the new environment, but when the ovaries of a young animal are transplanted into an old animal, they fail to cycle. However, if the ovaries are removed from an animal when it's young, so that it lives to the normal age of infertility without being regularly exposed to surges of estrogen, it will then be able to support normal cycles when young ovaries are transplanted into it. But if it received estrogen supplements throughout its life, transplanted young ovaries will fail to cycle.

The work of Desjardins and others has demonstrated that free radicals generated by interactions of estrogen and iron with unsaturated fatty acids are responsible for damage to brain cells (Desjardins, et al., 1992). The damaged inhibitory nerve cells allow the pituitary to remain in a chronically active state; in old rats, this can produce a state of constant estrus. Several groups (Powers, et al., 2006; Everitt, et al., 1980; Telford, et al., 1986) have shown that removal of the pituitary gland can greatly extend lifespan, if thyroid hormone is supplemented.

One of the animal "models" used to study hot flashes is morphine withdrawal. The model seems relevant to human hot flashes, because estrogen can stop the morphine withdrawal flushing, and estrogen's acute and chronic effects on the brain-pituitary-ovary system involve the endorphins and the opioidergic nerves (Merchenthaler, et al., 1998; Holinka, et al., 2008).

In young rats, sudden morphine withdrawal caused by injecting the anti-opiate naloxone, causes the tail skin to flush, with a temperature increase of a few degrees, and causes the core body temperature to fall slightly. However, old animals respond to the withdrawal in two different ways. One group responded to the naloxone with an exaggerated flushing and decrease of core temperature. The other group of old rats, which already had a lower body temperature, didn't flush at all (Simpkins, 1994). I think this provides an insight into the reason that menopausal treatment with estrogen can relieve some hot flashes--estrogen treatment might create a flush resistant state similar to that of the cooler old animals in Simpkins' experiment.

It has been known for a long time, from studies in animals and people, that estrogen lowers body temperature, and that this involves a tendency to increase blood flow to the skin in response to a given environmental temperature, that is, the temperature "set-point" is lowered by estrogen. Besides increasing heat loss, estrogen decreases heat production. These physiological effects of estrogen can be seen in the normal menstrual cycle, with progesterone having the opposite effect of estrogen on metabolic rate, skin circulation, body temperature, and heat loss. This causes the familiar rise in temperature when ovulation occurs. Occasionally, young women will experience hot flashes during the luteal phase of their menstrual cycle because of insufficient progesterone production, or at menstruation, when the corpus luteus stops producing progesterone.

Estrogen increases the free fatty acids circulating in the blood, and this shifts metabolism away from oxidation of glucose to oxidation of fat, and

it also reduces oxidative metabolism, for example by lowering thyroid function (Vandorpe and Kühn, 1989). These changes are analogous to those of fasting, in which metabolism shifts to the oxidation of fatty acids for energy, causes decreased body temperature, and in some animals leads to a state of torpor or hibernation.

Despite decreasing oxidative metabolism, estrogen stimulates the adrenal cortex, both directly and indirectly through the brain and pituitary, increasing the production of cortisol. Cortisol, by increasing protein turnover, can increase heat production, but this effect isn't necessarily sufficient to maintain a normal body temperature. It increases blood glucose, mainly by blocking its use for energy production, but the glucose is derived from the breakdown of muscle protein. It allows some glucose to be stored as fat. Sudden increases in the amount of glucose can lower adrenaline, and chronically excessive cortisol tends to suppress adrenaline. Cushing's syndrome (produced by excessive cortisol) commonly involves flushing and depression, both of which are likely to be related to the decreased action of adrenaline.

While the biological changes occurring at menopause and during hot flashes are very similar to some of the direct actions of estrogen, and although the menopause itself is the result of prolonged exposure to estrogen, very large doses of estrogen can, in many women (as well as in morphine addicted rats), stop the flushing. In some of the published animal experiments, effective doses of estrogen were about 2000 times normal, and in some human studies, the dose was 30 times normal. By blocking the production of heat, the estrogen treatments might be creating conditions similar to those in Simpkin's cooler old rats, which failed to flush during morphine withdrawal. Menopausal estrogen treatment is known to lower temperature (Brooks, et al., 1994).

Since the Women's Health Initiative publicized the dangers of estrogen, there has been some interest in alternative treatments for hot flashes. Since a reduced production of progesterone has been associated with hot flushes for several decades, it isn't surprising that it is now being tested as an alternative to estrogen. Recently, 300 mg of oral progesterone was found to be effective for decreasing hot flashes, and a month after discontinuing it, the hot flushes were still less frequent than before using it (Prior and Hitchcock, 2012). Previously, transdermal progesterone was found to be effective (Leonetti, et al., 1999).

One of the things progesterone does is to stabilize blood sugar. In one experiment, hot flashes were found to be increased by lowering blood sugar, and decreased by moderately increasing blood sugar (Dormire and Reame, 2003).

Hypoglycemia increases the brain hormone, corticotropin release hormone, CRH (Widmaier, et al., 1988), which increases ACTH and cortisol. CRH causes vasodilation (Clifton, et al., 2005), and is more active in the presence of estrogen. Menopausal women are more responsive to its effects, and those with the most severe hot flushes are the most responsive (Yakubo, et al., 1990).

The first reaction to a decrease of blood glucose, at least in healthy individuals, is to increase the activity of the sympathetic nervous system, with an increase of adrenaline, which causes the liver to release glucose from its glycogen stores. The effect of adrenaline on the liver is very quick, but adrenaline also acts on the brain, stimulating CRH, which causes the pituitary to secrete ACTH, which stimulates the adrenal cortex to release cortisol, which by various means causes blood sugar to increase, consequently causing the sympathetic nervous activity to decrease. Even when the liver's glycogen stores are adequate, the system cycles rhythmically, usually repeating about every 90 minutes throughout the day.

Sympathetic nervous activity typically causes vasoconstriction in the skin and extremities, reducing heat loss, but the small cycles in the system normally aren't noticed, except as small changes in alertness or appetite. With advancing age, most tissues become less sensitive to adrenaline and the sympathetic nervous stimulation, and the body relies increasingly on the production of cortisol to maintain blood glucose. Many of the changes occurring around the menopause, such as the rise of free fatty acids and decrease of glucose availability, increase the sensitivity of the CRH nerves, causing the fluctuations of the adrenergic system

to cause larger increases of ACTH and cortisol. Estrogen is another factor that increases the sensitivity of the CRH nerves, and unsaturated fatty acids (Widmaier, et al. 1995) and serotonin (Buckingham, et al., 1982) are other factors stimulating it. Serotonin, like noradrenalin, rises with hypoglycemia (Vahabzadeh, et al., 1995), and estrogen contributes to hypoglycemia, by impairing the counterregulatory system (Cheng and Mobbs, 2009).

With the reduced vasoconstrictive effects of the sympathetic nerves, and the increased activity of CRH, cyclic vasodilation under the influence of cortisol will become more noticeable. With the onset of menopause, and in proportion to the number and intensity of symptoms (on the Greene Climacteric Scale), the daily secretion of cortisol was increased (Cagnacci, et al., 2011).

Once the ideologically based doctrine of menopause as estrogen deficiency is discarded, it's possible to see its features as clues to the ways in which "stress" contributes to the age-related degeneration of the various systems of the body--not just the reproductive system, but also the immune system, the nutritive, growth, and repair processes, and the motivational, emotional, and cognitive processes of the nervous systems. The changes around menopause aren't the same for all women, but the ways in which they vary can be understood in terms of the basic biological principles of energy and adaptation that are universal.

Each type of cell and organ is subject to injury, and in some cases these injuries are cumulative. In the healthy liver, which stores glycogen, toxins can be inactivated, for example by combining with glucuronic acid, derived from the stored glucose. With injury, such as alcoholism combined with a diet containing polyunsaturated fats, the liver's detoxifying ability is reduced. Even at an early stage, before there is a significant amount of fibrosis, the reduced activity of the liver causes estrogen to accumulate in the body. Estrogen's valuable actions are, in health, exerted briefly, and then the synthesis of estrogen is stopped, and its excretion reduces its activity, but when the liver's function is impaired, estrogen's activity continues, causing further deterioration of liver function, as well as injury of nerves such as Desjardins described, and the systemic energy shifts and stress activations mentioned above.

Besides lowering the liver's detoxifying ability, stress, hypoglycemia, malnutrition, hypothyroidism, and aging can cause estrogen to be synthesized inappropriately and continuously. With aging, estrogen begins to be produced throughout the body--in fat, muscles, skin, bones, brain, liver, breast, uterus, etc. Polyunsaturated fats are a major factor in the induction and activation of the aromatase enzyme, which synthesizes estrogen.

Increased synthesis of estrogen, by aromatase, and decreased excretion of it, by the liver and kidneys, are only two of the processes that affect the influence of estrogen during aging. Cellular stress (chemical, mechanical, hypoxemic, hypoglycemic [Clere, et al., 2012; Aguirre, et al., 2007, Zaman, et al., 2006, Saxon, et al., 2007; Tamir, et al., 2002; Briski, et al., 2010]) increases estrogen receptors (which activate CRH and the stress response). The presence of estrogen receptors means that estrogen will be bound inside cells, where it acts to modify those cells. Before estrogen can reach the liver to be inactivated, it must be released from cells. Ordinarily, the cyclic production of progesterone has that function, by destroying the estrogen-binding proteins. Progesterone also inhibits the aromatase which synthesizes estrogen, and shifts the activities of other enzymes, including sulfatases and dehydrogenates, in a comprehensive process of eliminating the presence and activity of estrogen. At menopause, when the ovary fails to produce the cyclic progesterone, all of these processes of estrogen inactivation fail. In the absence of progesterone, cortisol becomes more active, increasing aromatase activity, which now becomes chronic and progressive. The decrease of progesterone causes many other changes, including the increased conversion of polyunsaturated fatty acids to prostaglandins, and the formation of nitric oxide, all of which contribute to the tendency to flush.

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*The limits of the belief system or consciousness of US medicine are nicely defined by the topics included in the *Index Medicus*, which was published from 1879 to 2004, by the Surgeon General's Office of the U.S. Army, the American Medical Association, and the National Library of Medicine, at different times. If you look up any important topic in physiology or biochemistry in an index of scientific publications such as

Biological Abstracts or *Chemical Abstracts*, and then look for the same subject in the Index Medicus, you will find some startling differences–long delays and antagonistic attitudes. At first the discrepancies seem ludicrous and hard to account for, but I think they can be explained by recognizing that the editors of medical journals consider science to be their enemy.

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Ray Peat's Newsletter

"... a meaningful model of Life has to exclude Randomness." G. Zajicek

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When energy fails: Edema, hypertension, heart failure sarcopenia, cramps, etc.

More than 100 years ago the idea of a morphogenetic field was proposed by A.G. Gurwitsch, as a way to explain the orderly movements of cells in embryos and growing tissues, and to understand the principles that cause cells to change appropriately when their location in the organism changes. For 30 years, the concept guided research in embryology, but also led to important discoveries in the biology of cancer, aging, wound repair, and other important areas. But by the late 1940s, a more abstract approach to biology, based on the gene doctrine of Mendel and Weismann, took charge of academic and governmental biological research. This ideology at first said that organisms are determined by unchanging units of inheritance, "genes," and later when genes were found to be susceptible to mutation, the changes were said to be always random. The Central Dogma of the ideology was that any meaningful, adaptive changes that occur in an organism can't influence the genes. For many years, adaptive changes were said to be nothing but changes in the size or function of existing cells, because the cells of the major organs of the body were supposed to be created before birth, or in infancy.

Besides the purely ideological commitment to the theory of genes, there were other influences that contributed to the culture of Molecular Biology. People learned histology from slides or pictures made by killing, hardening, dehydrating, and slicing parts of organisms. Biochemists studied the chemistry of life mainly by grinding cells or tissues, and extracting water soluble materials to study the actions of enzymes on various materials. These unrealistic artifacts filled the textbooks and the minds of generations of biologists and physicians. The culture of molecular biology used these artifacts to create theories of embryology and physiology, and holistic ideas such as the developmental field were disregarded.

The mental image of a living organism that has been created by that culture is simply wrong. The concept of a developmental field is essential for understanding embryology, because things that exist on a scale bigger than molecules and cells govern the functions of the molecules and cells, and the principles of embryology don't arbitrarily stop operating at birth, but can be seen to continue operating during maturity and aging. The interactions of cells with their environment are different at different stages of life, but there are commonalities that are extremely important.

The processes that govern the pregnant woman's blood circulation, in sustaining the development of a fetus, are very similar to the processes that govern anyone's blood circulation, providing for the maintenance and renewal of all the body's organs. The common problems of pregnancy involving the circulatory system can provide insights into the problems of the various organs that have been the focus of the medical specialties, and into some basic medical issues, including aging, obesity, and inflammation.

The development of a fertilized egg into an embryo consumes energy at a very high rate, and the way the embryo develops depends on a continuously adequate supply of oxygen and sugar, and other nutrients. The intense flow of energy through each stage of a developing structure shapes the following stage. The necessary energy and materials are provided abundantly by the mother's blood. When the development has advanced far enough to make life possible outside the uterus, energy will be used more slowly, for growth, maintenance, and renewal of tissues.

Failure to renew cells and tissues leads to the loss of function and substance. Bones and muscles get weaker and smaller with aging. Diminished bone substance, osteopenia, is paralleled, at roughly the same rate, by the progressive loss of muscle mass, sarcopenia (or myopenia). The structure of aging tissue changes, with collagen tending to fill the spaces left by the disappearing cells. It's also common for fat cells to increase, as muscle cells disappear.

When conditions are ideal, as during healthy development in the uterus, tissue damage is corrected by the multiplication of cells to replace any that were lost. But when conditions are less perfect, injuries are imperfectly repaired, usually with highly collagenous scar tissue bridging the area that was destroyed. During this imperfect repair, there is inflammation, which apparently exists to the extent that the substances needed for regeneration are lacking. For example, when oxygen is lacking, lactic acid is likely to be produced, along with increases of pro-inflammatory regulators such as histamine and serotonin, leading to the loss of many important proteins and functions, and the over-production of collagen instead.

Since cellular renewal of tissues, in a healthy individual, is a constant process, we can think of the metabolic rate of a healthy adult as just what is needed to sustain this constant, limited sort of regeneration, but not quite intense enough to produce scarless healing of a wound (without special intervention).

If something reduces the systemic ability to produce energy, there will be a gap between the available energy and the energy needed for the constant turnover of cells in each tissue and organ, and a generalized inflammation will develop. The replacement of cells will be slowed, and the organism will mobilize the processes used for producing scar tissue, producing an excess of collagen, filling the spaces left by the lost cells.

We are susceptible to many things that interfere with energy production---the substitution of iron for copper in the respiratory enzyme, the absorption of endotoxin, the accumulation of PUFA, a deficiency of thyroid hormone, the formation of increased amounts of nitric oxide, serotonin, and histamine, etc. Different environments will condition the way the defensive mechanisms of inflammation are produced.

Toxemia of pregnancy, or preeclampsia, is a state of generalized inflammation, and some of the causes and remedies are known. Despite the predominance of crazy genetic theories of preeclampsia in 20th century medical literature, there was clear evidence (reviewed by Tom Brewer, Douglas Shanklin, and Jay Hodin) that it was caused by malnutrition, and that it could be cured by adequate protein, salt, and calcium.

The old medical practice of restricting salt intake during pregnancy was an important factor in causing it, so it's interesting to look at the effects of salt restriction as a treatment for hypertension.

The pregnant woman's blood volume expands, to permit the supply of energy to match the needs of the embryo. If the blood volume doesn't increase, or if it decreases, as in pregnancy toxemia, her blood pressure will increase. Typically, the decrease of blood volume is accompanied by an increase in the extracellular fluid, edema, resulting from leakage of fluid through the walls of the capillaries, and albumin appears in the urine as it leaks through the capillaries in the kidneys. The amount of blood pumped by the heart, however, is increased in toxemia (Hamilton, 1952), showing that the increased blood pressure is at least partially compensating for the smaller volume of blood.

A similar situation, reduced blood volume and edema, can be seen (Tarazi, 1976) in "essential hypertension," the "unexplained" high blood pressure that occurs more often with increasing age and obesity. At the beginning of "essential hypertension," the amount of blood pumped is usually greater than normal.

In both situations, preeclampsia and essential hypertension, there is an increased amount of aldosterone, an adrenal steroid which allows the kidneys to retain sodium, and to lose potassium and ammonium instead. A restriction of salt in the diet causes more aldosterone to be produced, and increased salt in the diet causes aldosterone to decrease. One effect of aldosterone is to increase the production of a substance called vascular

endothelial growth factor, VEGF, or vascular permeability factor, which causes capillaries to become leaky, and causes new blood vessels to grow.

While increased salt in the diet tends to lower both aldosterone and VEGF, reducing the leakiness of blood vessels, sodium also has a direct effect that tends to prevent the leakage of water and albumin out of the blood vessels, helping to maintain the blood volume which is needed to perfuse the kidneys, preventing them from producing signals to increase blood pressure and aldosterone. There is a large amount of albumin in the blood serum, and sodium ions associate with the negative electrical charges on the albumin molecule. This association causes the complex of albumin and sodium to attract a large amount of water, that is to exert osmotic or oncotic pressure. This oncotic pressure causes any excess extracellular water to be attracted into the blood vessels, preventing edema while maintaining the blood volume. When there is too little sodium, the albumin molecule itself easily leaves the blood stream along with the water.

Instead of considering the significance of sodium's effects on albumin, aldosterone, and VEGF, textbooks have often talked about the factors that "pump" sodium, and factors that specifically regulate the movement of water. Experiments in which an excess of aldosterone is combined with a high salt intake produce increased blood pressure, and--by invoking various genes--salt is said to cause hypertension in certain people. This reasoning is hardly different from the reasoning of the drug companies in the 1950s who said that since women with toxemia have hypertension and edema, they should be treated with a diuretic and a low salt diet, to eliminate water and to reduce blood pressure.

The physiological loss of sodium occurs when energy metabolism fails, as in diabetes, hypothyroidism, hyperestrogenism, and starvation. What these conditions have in common is an increased level of free fatty acids in the blood. Increased free fatty acids impair the use of glucose. The consumption of carbohydrate, like an increase of thyroid hormone, insulin, or progesterone, increases the retention of sodium; fructose is the most effective carbohydrate (Rebello, et al., 1983).

The loss of sodium is often accompanied by the retention of water, reducing the osmotic pressure of the body fluids. The leakiness of blood vessels allows the extracellular fluid volume to increase, as understood in the standard definition of edema. However, when this fluid is hypo-osmotic, it will enter cells, causing them to swell. Cell swelling excites cells (Ayus, et al., 2008; Baxter, et al., 1991), and can kill them if they are unable to produce enough energy to restore their original volume, by measures including the excretion of amino acids and potassium. Both low sodium (hyponatremia) and low osmotic pressure stimulate the adrenergic nervous system.

The increase of adrenalin, caused by a deficiency of sodium, is one of the factors that can increase blood pressure; if the tissues's glycogen stores are depleted, the adrenalin will mobilize free fatty acids from the tissues, which tends to inhibit energy production from glucose, and to increase leakiness. After I had read Tom Brewer's work on preventing or curing preeclampsia with added salt, I realized that the premenstrual syndrome involved some of the features of preeclampsia (edema, insomnia, cramps, hypertension, salt craving), so I suggested to a friend that she might try salting her food to taste, instead of trying to restrict salt to "prevent edema." She immediately noticed that it prevented her monthly edema problem. For several years, all the women who tried it had similarly good results, and often mentioned that their sleep improved. I mentioned this to several people with sleep problems, and regardless of age, their sleep improved when they ate as much salt as they wanted. Around that time, several studies had shown that salt restriction increases adrenalin, and one study showed that most old people on a low sodium diet suffered from insomnia, and had unusually high adrenalin. When they ate a normal amount of salt, their adrenalin was normalized, and they slept better.

It's very common for physicians who are aware of progesterone's "anti-aldosterone" activity to think that both estrogen and progesterone are responsible for the increased risk of sodium loss in women, especially during pregnancy, but Hans

Selye demonstrated that progesterone will normalize sodium retention even when there is no aldosterone at all, following removal of the adrenal glands. It is estrogen which is responsible for the dangerous loss of sodium.

The ratio of estrogen to progesterone--regardless of age or gender--is an important factor in regulating minerals and water, cell energy metabolism, and blood pressure. The ratios of many other regulatory substances (including serotonin/dopamine, glucagon/insulin, and aldosterone/cortisol+progesterone) vary according to the quality of the individual's level of adaptation to the environment. Improving the environment can shift the ratio in the direction of restoration, rather than mere survival.

Gershom Zajicek and his colleagues have demonstrated an organized renewal of tissues, in which new cells are born with the division of stem cells, and "stream" away from their origin as they mature, and finally are shed or dissolved. A few studies have demonstrated a similar kind of migration of new cells in the brain (Eriksson, et al., 1998; Gould, et al., 1999), a process which differs by the absence of systematic dissolution of mature brain cells. While Zajicek has demonstrated the conversion of one kind of cell, such as a pancreatic ductal epithelial or acinar cell into insulin-secreting beta cells, other researchers have shown that after injury to the pancreas beta cells can be formed from glucagon-secreting alpha cells, as well as from other beta cells.

Stress, increasing the need for energy, increases the formation of cortisol and free fatty acids when glucose isn't available, and those--while they provide alternative sources of energy--interfere with the ability to produce energy from glucose. Free fatty acids and cortisol can cause the insulin-secreting beta cells to die. Glucose, and insulin which allows glucose to be used for energy production, while it lowers the formation of free fatty acids, promote the regeneration of the beta-cells. Although several research groups have demonstrated the important role of glucose in regeneration of the pancreas, and many other groups have demonstrated the destructive effect of free fatty acids on the beta cells, the mainstream medical culture still claims that "sugar causes diabetes."

In the adrenal glands, renewing cells stream from the capsule on the surface of the gland toward the center of the gland. The first cells to be produced in a regenerating gland are those that produce aldosterone, the next in the stream are the cortisol producing cells, and the last to be formed are the cells that produce the sex hormones, the androgens including DHEA, and progesterone. In aging, after the age of thirty, the renewal slows, but the dissolution of the sex hormone zone continues, so the proportion shifts, increasing the ratio of the aldosterone and cortisol producing cells to the layer that produces the protective androgens and progesterone (Parker, et al., 1997).

Even before aldosterone was identified, progesterone's role in regulating the salts, water, and energy metabolism was known, and after the functions of aldosterone were identified, progesterone was found to protect against its harmful effects, as it protects against an excess of cortisol, estrogen, or the androgens. New anti-aldosterone drugs are available that are effective for treating hypertension and heart failure, and their similarity to progesterone is recognized.

While stress typically causes the adrenal glands to produce cortisol, extreme stress, as described by Hans Selye, damages the adrenal cortex, and can cause the cells to die, leading to the death of the animal. There is evidence that it is the breakdown of unsaturated fatty acids that causes damage to the adrenal cortex in extreme stress. Although many factors influence the production of the adrenal steroids, arachidonic acid, even without being converted to prostaglandins, is an important activator of aldosterone synthesis. Adrenalin, produced in response to a lack of glucose, liberates free fatty acids from the tissues, so when the tissues contain large amounts of the polyunsaturated fatty acids, the production of aldosterone will be greater than it would be otherwise.

The continuing accumulation of polyunsaturated fats in the tissues is undoubtedly important in the changing relationship between the pancreas and the adrenal glands in aging. Aspirin, which is antilipolytic, decreasing the release of free fatty

acids, as well as inhibiting their conversion to prostaglandins, lowers the production of stress-induced aldosterone, and helps to lower blood pressure, if it's taken in the evening, to prevent the increase of free fatty acids during the night. Aspirin increases insulin sensitivity. A low salt diet increases the free fatty acids, leading to insulin resistance, and contributing to atherosclerosis (Prada, et al., 2000; Mrnka, et al., 2000; Catanozi, et al., 2003; Garg, et al., 2011).

The same factors that support or interfere with cellular renewal in the pancreas and adrenal glands have similar effects in the bones, skin, skeletal and heart muscle, nervous system, liver, and other organs. In every case, the local circulation of blood is influenced by both local and systemic factors. The loss of control over the water in the body is the result of energy failure, and hypertension is one of the adaptations that helps to preserve or restore energy production.

Lowering inflammation and the associated excess of free fatty acids in the blood, and improving the ability to oxidize glucose, will lower blood pressure while improving tissue renewal, but lowering blood pressure without improving energy production and use will create new problems or intensify existing problems. After 40 years the medical profession quietly retreated from their catastrophic approach to pregnancy toxemia, but in the more general problem of essential hypertension, the mistaken ideology is being preserved, even as less harmful treatments are introduced. That ideology prevents a comprehensive and rational approach to the problems of stress and aging.

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Ray Peat's Newsletter

Medical genetics and immunology: Islands of fantasy in a sea of ignorance

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Implications of inflammation

It has become widely accepted that inflammation has a central role in several major diseases--atherosclerosis, cancer, Alzheimer's disease, diabetes and obesity, Parkinson's and Huntington's disease, asthma, epilepsy, for example--so understanding the nature of inflammation has gained special importance. For thousands of years, inflammation has been defined by the presence of swelling, redness, increased heat, and pain.

Is the inflammation the main cause of the disease, or is it instead, a response to the disease process? Not long ago, the medical profession began to see inflammation as an important part of the healing process, reflecting the actions of both an innate immunity and a learned immunity, and before that, it was seen, like fever, as the problem to be relieved, with "allopathic" treatments.

Soon after good microscopes were developed, Rudolf Virchow described the collection of white blood cells in infected areas and tumors, and suggested that their accumulation was a consequence of the damage to blood vessels and congestion, caused by tissue damage. They were incidental to the inflammation. A generation later, Elie Mechnikoff, who had studied the orderly and meaningful movements of cells in the developing embryos of a great variety of organisms, saw that the collection of white cells around a foreign material was intentional; in the case of the embryos of starfish, the white cells were part of the organism's digestive system. When he introduced rose thorns into the tissues of water fleas, the wandering cells engulfed and dissolved them. He reasoned that the pus that surrounds a thorn in a person's finger represents the same process--a protective eating and destruction of the harmful material.

For the Greeks and Romans, the pus of an abscess was "laudable," but by Mechnikov's time, pus had become identified with the presence of infectious microorganisms. Disinfectants were used to prevent the infections that could produce pus. However, by the end of the 19th century, sterile extracts of microorganisms were found to be able to produce the inflammatory signs of infection. Virchow's observation of white blood cells in cancers could be considered as an early recognition of sterile inflammation, but the term came into use later, and has appeared intermittently in the literature for many years. The concept has become more important as researchers have explored the interactions between the supposedly primitive, non-specific "innate immunity," and the supposedly more highly evolved specific adaptive immunity.

Trauma, prolonged interruption of blood supply, chemical injury, radiation injury, and signals from nerves are among the things that can cause sterile inflammation.

Although the concept of sterile inflammation has been in the medical literature for a long time, the influence of the drug industry has helped to keep it from entering significantly into medical education. In 1976, I was talking to a recent graduate of Stanford's medical school, and when I mentioned sterile inflammation, she interrupted, saying "there's no such thing, inflammation means that there's an infection." When the involvement of inflammation in neurological disease or atherosclerosis is mentioned, most physicians probably infer that this is evidence of a hidden infection or a mysterious new organism. It could be, but to assume that is to neglect the many other possible causes.

Mechnikov's idea of intentionality, goal directed behavior, in the wandering cells was antagonistic to the most powerful trend in science,

the doctrine of randomness in a mechanistic, deterministic view of matter. Following Descartes, the mechanistic materialists saw living organisms as machines, in which each part interacts mechanically with adjoining parts, and consciousness was something essentially distinct from the living substance of the organism. But as early as the 18th century, some researchers were thinking of the brain as an integrating center, not only for perception and movement, emotion and thought, but even for sickness and health.

The mechanistic materialists labeled such holistic thinking as anthropomorphizing or vitalism. Explanations were considered to lack "objectivity" if they related to a purpose; students were taught to avoid "teleological" explanations, if they wanted to be real scientists. However, from the time of Pasteur and the adoption of mass vaccination, the body's reactions to alien material were concretized in the concept of an "immune system," which existed for the purpose of defending against infections. It's important to remember what scientific knowledge about the nature of life was at that time--almost nothing that people believed at that time about how our bodies come into being, how they produce chemical changes, or how they move and sense, is now recognized as true. But the basic idea of an "immune system" has hardly changed in 100 years.

Although Mechnikov shared the 1908 Nobel Prize with Paul Ehrlich, Ehrlich's Nobel lecture expressed an extremely reductionist view of the organism, almost comical when juxtaposed to Mechnikov's lecture. According to Ehrlich, it was necessary for science to differentiate "the concept of the cell into that of a great number of separate, individual functions." In that lecture he talked about lock-and-key interactions, and receptors on cells. This was the course taken by science in the following century.

Mechnikov's goal directed phagocytes were accepted as part of the immune system that increasingly focused on Ehrlich's highly specific antigens and antibodies. Although the immune system was understood to have the purpose of defending the organism by destroying germs, it was put into an "objective" reductionist mechanistic scheme by giving it its own evolutionary explanation, through the natural selection of random changes in genes which, through time, became a very complicated machine that happened to kill germs, by strictly local molecular interactions. The germ killing, antibody forming immune system was thought to have evolved bit by bit, along with the evolution of the complex nervous, reproductive, and digestive structures and functions that distinguish mammals and people from sponges and roundworms, each feature the result of random changes that were preserved by natural selection.

By the 1960s, because of the ability through "vaccination" to create antibodies that would bind even to newly synthesized substances, the earlier idea of a simply genetically programmed immune system had to be abandoned, because the number of possible antibodies would have required a tremendous amount of DNA, that wouldn't fit inside a cell. New genetic explanations were invented to explain the ability of the immune system to adapt flexibly to unexpected new diseases. This was achieved by the idea of the immune system as a microcosm of evolutionary history, in which hypermutable genes could in a very short time evolve the new sequences needed to produce novel antibodies to destroy novel pathogens. It was still random, but very fast, and the cells that were selected, and stimulated to multiply, formed a clone, the way a mutant cancer cell formed a clone, supposedly giving each tumor its unique genetic individuality.

In an international immunology symposium at the University of Oregon in 1969, a few famous immunologists presented their recently developed theory about immunity, based on the neodarwinian theory of evolution as the result of random changes that are preserved by natural selection. The day after a description, to a large audience, of an experiment demonstrating clonal selection, in which specific immune cell clones were killed in a culture dish, and shown to stay dead, while other clones survived, an assistant professor of developmental biology described, to a small group of students, an experiment in which he had replicated that demonstration of clonal selection, and then repeated the same conditions, but with different concentrations of cells in the dish. With a sparse

cell population in the dish, his results were the same as those described in the earlier lecture, but when he increased the cell population to a certain point, the missing "clones" reappeared.

In the absence of a whole organism, but with a quorum of their peers, the cells were able to reconstitute a full repertoire of sensitivity. My impression as he described the experiment was that it implied that each cell had to have a knowledge of the type of organism it belonged to, rather than just being committed to expressing certain genes for the rest of its life. A few weeks later I met the professor in the hall and asked if he was publishing the experiment, and he said he hadn't written it up yet. I watched for it in the next few years, but never saw anything by him that related to it. Ten years later, a few other people began questioning the clonal deletion theory of self tolerance, but the many changes that have been made subsequently have been essentially to preserve the mechanistic randomness of the theory, and the doctrine that it is a system specifically evolved for fighting microbes. The goal-directedness introduced by Mechnikov was kept for the system as a whole, but the intentionality was reduced to random changes.

This doctrine of a separately evolved, and evolving, immune system provided no insight into the phenomenon of sterile inflammation, and it's that kind of inflammation, which lacks intelligible goal-directedness, that has become so important for understanding the chronic and degenerative diseases, and aging.

Before someone thinks of a mechanistic-neodarwinist theory of sterile inflammation, I want to propose a very different approach. Life is very adaptable, but it isn't infinitely adaptable. Life, in its highly complex forms, whether mollusk, mammal, fungus, or phanerogam, has many common features, and each type has a range of environments that are more or less suitable. The neodarwinian ideology inclines many biologists to assume that an organism's present form represents its best adaptation to its present environment, or to its recent past environments. This leads to arguments that "we evolved to eat ...," or to live in certain ways. But experiments in which animals become more intelligent and live longer when they are put into an environment which never existed in nature imply that organisms have their own internal principles that allow them to become more than they or their ancestors ever were, if they have the right environment.

The intrauterine environment permits injuries to be repaired, mostly without inflammation or scarring, and when some of those features, such as high carbon dioxide and sugar content are provided postnatally, inflammation and scarring can be prevented or reduced.

When prenatal environments are modified, the development of the animal's brain and metabolism is affected, affecting the course of that animal's life, and influencing subsequent generations. The wrong balance of prenatal nutrients can decrease the metabolic rate and increase obesity, or a better balance can increase brain development and alertness. When a young animal's early life is enriched with stimulation and opportunity for exploration, its brain development is improved (increased cortical thickness and enzyme activity), and those changes are passed on to subsequent generations, with cumulative effects if the improved environment continues to be available.

The prenatal absence of inflammation corresponds to conditions that are providing energy and other conditions necessary for a very high rate of metabolism, with minimal stress. Generalizing from an understanding of gestation, we could say that inflammation, and the failure of tissue maintenance, occurring later in life is the result of a gap between the energy that's available and the demands that are made on the organism or on a particular tissue.

This approach to understanding inflammation suggests why it contributes to degenerative processes, and suggests potential remedies, but it also offers a new perspective on the processes that are called innate and acquired immunity. The boundaries of what used to be called an immune system have been expanding and becoming blurred, as the interactions of nerves, hormones, nutrition, tissue repair, reticulo-endothelial system, phagocytosis, and wandering or stem cells come to be understood in more detail.

Jamie Cunliffe and Polly Matzinger have been developing a new understanding of the immune

system, centered on the idea that tissue damage is the main issue, rather than the distinction between self and nonself antigens. They recognize that the old model, especially the "adaptive immune system," is failing to explain things, and they are giving more weight to things such as inflammation that had been attributed to an "innate immune system," but what they are describing might better be described as an alert, intelligent organism maintaining itself.

This new orientation would make "stem cells" part of the "immune system," since they sense danger or tissue damage, and adapt to repair it. The wandering white blood cells, rather than being the end product of a particular clone, are able to transform themselves when they find themselves in new situations, becoming a different kind of cell. The signals that cause them to go where they are needed are related to inflammation, but this is exactly where immunology and stem cell research need to direct their attention. These signals are strongly influenced by environmental conditions.

One of the important features of the intrauterine environment is that it is steadily very warm, and that means that the fats which are synthesized from sugar will be relatively saturated. If sugar is deficient, which is common as a result of maternal hypoglycemia in the third trimester of pregnancy, free fatty acids from the mother's tissues and her diet will provide energy for the fetus.

The brain requires a high level of sugar for optimal growth, so maternal undernutrition or hypoglycemia will increase the ratio of the baby's body weight to its brain weight, and will change various other features of metabolism and structure. If the mother's fats are highly unsaturated, they can be turned into the pro-inflammatory prostaglandins during stress, and hypoglycemia during the third trimester is highly stressful for the fetus. Besides causing injury to the fetus during this time, producing inflammation and potentially scarring and granuloma or fibroma formation, the prostaglandins activate the stress hormones, such as corticotropin release hormone, which is a trigger for stimulating the birth process, and so tend to cause premature delivery.

These polyunsaturated fats, which are clearly alien to the gestational process, interfering in so many ways with optimal development, are present in the mother's tissues and foods because of the type of environment she occupies. If she ate only foods from a warm climate, where plants and animals produce mostly saturated fats, the fetus wouldn't be subjected to the anti-regenerative, pro-inflammatory, anti-developmental effects of the fatty acids and prostaglandins. The polyunsaturated fatty acids, prostaglandins, and inflammation, clearly encroach on the process of gestation, altering the subsequent life of the exposed individuals, causing them to adapt to the world by metabolizing less energy; they continue to constrain development throughout the lives of those who continue to be exposed to them.

The figures for premature births and low birth weight in recent decades suggest the importance of the issue. While adults are getting fatter, more underweight babies are being born. In affluent countries, while the adults' body size has increased during this time, their head circumferences haven't. These changes are similar to those seen in animals fed increased amounts of polyunsaturated fats. Besides being the precursors for the prostaglandins, the polyunsaturated fatty acids amplify inflammation and stress in a variety of other ways.

The prostaglandins are, in adults as they are in the fetus, central to the scarring, fibrosis, and failure of regeneration that are considered to be normal for mammals when they are injured or are aging. The failure of regeneration in a phylum of animals is closely related to their susceptibility to forming tumors. Cancer can be considered as a form of dystrophy, a consequence of tissue atrophy, a failure to keep regenerating. An example of this antagonism would be the experiment in which parts were cut off salamanders, allowing them to grow a new tail or leg, but when a tumor was grafted on where a tail was amputated, the tumor was converted into a tail, by the animal's "regenerative environment."

Before the recognition that adult tissues all contain stem cells, most biologists thought of the organism as being made up of "adult cells," that would last for a large part of a normal life span. Tissues were examined microscopically after they had been killed and hardened chemically, and it didn't occur to most researchers to think of the

image under the microscope as a single frame from a moving picture. G. Zaijecek has done experiments that reveal "cell streaming" in tissues normally thought of as static, such as the liver, pancreas, or the cornea of the eye. It has been recognized for a long time that when the cells of the adrenal cortex are regenerating they "stream" away from the outer capsule, changing their form and function as they go. Zajicek has showed evidence that a similar transformation of function occurs in the pancreas, with acinar cells turning into islet cells as they migrate (Zajicek, et al., 1990).

The innervation of some regenerating epithelial tissues, such as the bladder, skin, and cornea, has been studied in considerable detail, and it's fairly well known that the sensory nerves have complex "trophic" or sustaining effects in these tissue. For example, if sensory nerves are destroyed in an area of the skin, that area becomes thin and shiny. Since some of Pavlov's earliest studies, nerves have been known to have a trophic function on the tissues they innervate. In some tissues--bladder, stomach, heart, liver--complex chemical signals are known to be released by the sensory nerves, but the presence of nerves in other tissues, such as the cortex of the adrenal gland (Heym, et al., 1995), hasn't been so well studied, though all such tissues are known to have nerves. In animals such as salamanders, nerves are known to be involved in the regeneration of lost parts. Nerves are intrinsic parts of cancers, too.

About 50 years ago, a study of the production of blisters produced by hypnotic suggestion found that the blister fluid contained ATP, which had been released by sensory nerves, at the spot that had been touched by what the subject believed was a lighted cigarette. ATP also appears in the fluid of a blister caused by heat, but this example showed how important the sensory nerves are, for things beyond sending messages to the brain. Both ATP, and one of its breakdown products, adenosine, activate some enzymes involved in inflammation. ATP activates the MMP proteinase enzyme that dissolves extracellular matrix, which is a basic step in tissue remodeling, and it also activates a phospholipase which releases arachidonic acid, and the cyclooxygenase enzyme, COX-2, which converts arachidonic acid to prostaglandins.

Besides activating the enzymes to break down the extracellar structure, ATP stimulates cell division and angiogenesis, all of which are normal parts of tissue maintenance. In the bladder, stretching causes the epithelial cells to release ATP, which stimulates sensory nerves; in this situation, the epithelial cells are acting as sense organs, and the ATP acts as a neurotransmitter. It has a similar effect in the breast, in relation to milk ejection (Bowler, et al., 2001). In other tissues, such as bone, mechanical forces also release extracellular ATP, and in this situation it seems to be an important anabolic stimulus to bone growth and repair (Furuya, et al., 2004).

ATP is increasingly recognized (Burnstock, 2007) as a basic neurotransmitter or cotransmitter, but it is something more important and basic than that: it's a constant signal of any cell's presence to neighboring cells. If the concentration of ATP varies too much, it indicates that something is wrong. If a cell is injured or fails to produce enough energy, it leaks ATP. During oxygen deficiency, the leaking ATP causes vasodilation, increasing circulation, and in the respiratory center, it stimulates breathing (Buttigieg and Nurse, 2004; Conde, et al., 2012).

In the prenatal environment, lacking polyunsaturated fatty acids from the environment, ATP is involved in the orderly development of the organism, adjusting rates of growth in a coordinated way. This system, that can be seen in embryology and the early stages of gestation, has all the properties of a self-regulating control system, with a built-in intention to develop in a certain direction. The intention that Mechnikov saw in the phagocyte, is in the whole organism. Cells that will later be thought of as part of "the immune system" are present at the very early stages of embryonic development, participating in its coming into existence. There is no genetic "blueprint" that is being read out for either the organism as a whole or for an immune system that has evolved to deal with infectious challenges. The system creates and discovers its potential, in a unique way, responding to what its environment provides it.

Not long ago, following the cult of the "Weismann barrier," it was believed that oocytes were "read out" at an early stage of development, from a genetic blueprint that would never be accessible again. That doctrine lasted for 100 years, until someone tested it (Johnson, et al., 2004, 2005; Bukovsky, et al., 2005; White, et al., 2012). As they showed, the embryo and the adult are intentional unities, able to improvise in surprising ways, but genetics and immunology have created fragmentary, mechanistic descriptions of them.

During development, the coordinated growth and functioning of the system is affected by the chemicals in the environment that the organism encounters. The prostaglandins reflect a particular ecosystem in which plants produce certain unsaturated fatty acids, but biomedical ideologues have idealized them, following the doctrine that this is the environment that we evolved to live in. This is very much like the nutrition professor at Oregon State University who taught students that white bread should be included in the diet because God gave it to us.

Lacking PUFA and prostaglandins, extracellular ATP would activate constructive pathways, tending to create a new equilibrium, without producing all of the harmful effects of the prostaglandins. As unstable polyunsaturated fats accumulate in the tissues with aging, they increasingly promote vicious circles of stress (some of those were described in Fats, Functions & Malfunctions).

Recognizing a mismatch between the organism's potentials and the present environment, and suggesting ways to improve the environment, isn't anything new, and a limited form of it has been institutionalized in various offices of occupational health and safety, traffic safety, and pollution control, but it conflicts with the other well-institutionalized attitude, that people must be changed to conform to the situation as it is. Eugenics, sterilization, vaccination, health education, and publicity campaigns explaining why cancer, heart disease, and obesity are caused by choices the individual makes, are well financed and supported by large organizations.

The idea of autoimmunity epitomizes this general situation, in which reductionist theories are invoked to explain why a person is causing his own sickness. If antibodies evolved to attack microbes, then the immune system has become defective when it produces antibodies against its own tissue. But if the system of wandering cells, complement, antibodies, etc., has to do with development and maintenance of the organism, the presence of antibodies and other "immune" factors would be expected whenever a tissue is damaged.

Simply twisting a piece of cartilage has been shown to make it antigenic, and many other things causing sterile inflammation cause antibodies to appear. Strokes or other brain injuries cause antibodies to be produced. The presence of auto-antibodies has been found to facilitate the recovery from an aseptic inflammatory condition of the brain, accelerating healing and re-vascularization (Hofstetter, et al., 2003). Intravenous immunoglobulin has a long history of use to reduce inflammation (Nimmerjahn and Ravetch, 2008), and it has been tested as a treatment for heart failure, producing anti-inflammatory effects (Aukrust, et al., 2006).

Components of the complement system and C-reactive protein, which are increased by tissue injury, are involved in the anti-inflammatory clearance of dying cells (Gershov, et al., 2001).

The presence of the "essential fatty acids" is an important factor in the allergenicity of transplanted tissues (Schreiner, et al., 1988), which might be expected, from the role of the prostaglandins in creating inflammation whenever a tissue is stressed.

Many types of evidence indicate that environmental PUFA and prostaglandins produced from the "essential" fatty acids are required for inflammation to progress to degeneration. The n-9 polyunsaturated fatty acids (the kind that we can make from saturated fat or sugar) seem to be positively protective against inflammation. For example, rats fed a diet with 2% hydrogenated coconut oil for two weeks had lower levels of IL-6 and C-reactive protein than when a small amount of arachidonic acid and docosahexaenoic acid (DHA) were added. Mead acid (20:3n9) was lower in the group with the PUFA supplement,

and the inflammatory reaction to endotoxin was greater in the supplemented group (Ling, et al., 2012).

Many of the things that can be achieved by vaccination and treatment with safe anti-inflammatories such as aspirin could be done better by long-term changes of diet, and by taking into account the interactions of the hormones, especially progesterone, estrogen, and thyroid, with nutrients and stressors. But much more than that is needed: The nature of the relationships between environmental factors and the body's reactions has to be clarified, so that the processes of healing and regeneration can more closely resemble the prenatal condition, possibly even continuing in adulthood the "pedomorphic" process, realizing human potentials that haven't previously been seen.

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